

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ :

A61K 9/20

A1

(11) International Publication Number:

WO 00/10536

(43) International Publication Date:

2 March 2000 (02.03.00)

(21) International Application Number: PCT/US99/19260

(22) International Filing Date: 24 August 1999 (24.08.99)

(30) Priority Data:

60/097,843	25 August 1998 (25.08.98)	US
Not furnished	23 August 1999 (23.08.99)	US

(71) Applicant (for all designated States except US): COLUMBIA LABORATORIES, INC. [US/US]; Suite 400, 2875 North-east 191 Street, Aventura, FL 33180 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BOLOGNA, William, J. [-/FR]; 22, place de General Catroux, F-75017 Paris (FR). LEVINE, Howard, L. [-/US]; 107 Balsam Street, Oceanside, NY 11572 (US). CARTIER, Philippe [-/FR]; 19, rue du General Foy, F-75008 Paris (FR). DE ZIEGLER, Dominique [-/FR]; 6, rue de la Source, F-75016 Paris (FR).

(74) Agents: KOCH, Robert, J. et al.; Fulbright & Jaworski L.L.P., 801 Pennsylvania Avenue, N.W., Washington, DC 20004-2604 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.

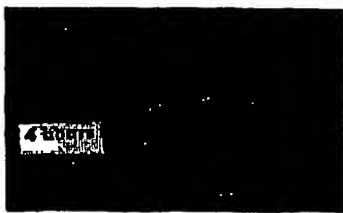
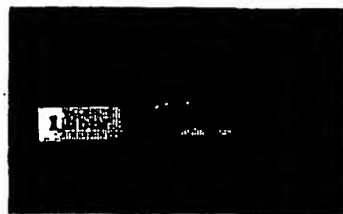
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: EXTENDED RELEASE BUCCAL BIOADHESIVE TABLET

(57) Abstract

A bioadhesive tablet wherein the active ingredient may be protected from water or the surrounding environment, thereby protecting it from metabolism or from other degradation caused by moisture, enzymes, or pH effects, and making it bioavailable only at a controlled rate. The active ingredient may be protected from moisture during the manufacturing process and more importantly may be protected from moisture and the immediate septic environment until after the patient has applied the tablet, and then only at a slow and controlled rate. It is by this process of progressive hydration that the active ingredient remains protected for many hours after administration. It is also by the process of progressive hydration that controlled and sustained release is achieved because only that part of the active ingredient that is the hydrated (aqueous) fraction of the tablet is available for absorption (bioavailable).

BIOADHESIVE PROGRESSIVE HYDRATION TABLET



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LÜ	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

EXTENDED RELEASE BUCAL BIOADHESIVE TABLET**BACKGROUND OF THE INVENTION****1. Field of the Invention**

5 The present invention relates to a bioadhesive, bioerodible tablet for the extended and controlled release of active ingredients. More particularly, the present invention relates to a progressive hydration tablet for adhesion to the wall of a body cavity for the sustained release of active ingredients without premature degradation of the active ingredients caused by
10 metabolism, or by moisture, enzymes or pH effects.

2. Description of the Related Art

 Medications and other pharmaceutical products have traditionally been administered in doses via oral ingestion, nasal sprays or injections. These delivery methods have proven ineffective for patients needing a prolonged and constant supply of an active ingredient delivered
15 to the bloodstream. Particularly difficult are patients needing dosing during sleep time hours. For these patients, intravenous venous lines, slow-dissolving pills, and suppositories or transdermal patches have been prescribed. However, the inconvenience and discomfort of IVs, the short life span of many ingested active ingredients from gastrointestinal degradation or first-pass liver metabolism, and the inability of many products to be comfortably delivered
20 transdermally in suitable doses or in controlled concentrations have proven these methods unsatisfactory.

 Previous artisans have attempted to meet the needs of the art by developing products for the transmucosal administration of active ingredients. For example, certain active ingredients can be administered quickly into the bloodstream via the walls of a body cavity, such as the

buccal or vaginal cavities, without the risk of first pass hepatic degradation. Generally, delivery of active ingredients through mucosal surfaces may be enhanced by the use of bioadhesive formulations. However, one particular area where those in the art have attempted, but heretofore failed, to meet the needs of the art is in developing a bioadhesive tablet useful for sustained release applications without risking degradation of the active ingredient before it is actually released.

"Sustained release" generally refers to continuous or sporadic release of an active ingredient over an extended time after a single administration, whereby the level of active ingredient available to the host patient often is maintained at some constant level over a period of time. As used herein, it is also intended to cover the situation where the release of an active ingredient is controlled over a period at time wherein the level of active ingredient available to the host (bioavailable) may be at a variable but predetermined level at a particular instant in time of treatment.

The sustained release bioadhesive tablets known in the art can be generally broken down into two categories: (1) tablets consisting of water soluble carbomers, and (2) tablets consisting of insoluble polymers. Both types of tablets have proven unsatisfactory for many applications. For example, numerous artisans have attempted to formulate a suitable sustained release bioadhesive tablet from water soluble carbomers, such as carbomer 934P or CARBOPOL™ 974 resin (commercially available from B.F. Goodrich, Cleveland, Ohio). However, such tablets often are only able to adhere to the wall of a body cavity for short periods of time, e.g., six hours or less. Also, these tablets are easily dislodged from the wall of a body cavity and thus place patients using such tablets buccally at risk of asphyxiation. Furthermore, these prior art tablets inherently become hydrated relatively quickly and thus may prematurely expose the reservoir of

active ingredient to degradation by moisture or by enzymes from the host environment such as from bacteria in the septic oral or vaginal cavities.

Similarly, tablets comprised of insoluble polymers, such as polycarbophil, have proven unsuitable for many applications. For example, although polycarbophil tablets are capable of prolonged attachment to the wall of a body cavity, such tablets do not adhere immediately, making them impractical for certain treatments such a buccal delivery of active ingredients to patients during sleep time hours. Further, such tablets often do not soften sufficiently to provide comfort and imperceptibility, or provide safety from potential aspiration of the tablet.

Furthermore, for example, neither type of prior art tablet is particularly suitable for treating many conditions. As alluded to previously, there are numerous medical conditions in which a sustained and/or controlled release of active ingredient(s) is desired for any of numerous reasons including, for example, to alleviate the impact of first-pass hepatic metabolism of the active ingredient or the risk of premature degradation of the active ingredient by moisture, pH effects, or enzymes, or to attain the comfort and convenience offered by a suitable bioadhesive tablet. Such conditions include, but are not limited to, for example, those needing treatment with an active ingredient that may be, but is not limited to, a glycoprotein, protein, sex hormone, anti-hormone, nitrate, beta-agonist, beta-antagonist, opioid, opioid-antagonist, antidepressant, HMG CoA (3-hydroxy-3-methylglutaryl Coenzyme A) reductase inhibitor, antihistamine, ACE (angiotensin converting enzyme) inhibitor, and/or prostaglandin. Heretofore the art has required such patents to undergo the more invasive and less suitable techniques and methods of delivery described above.

To illustrate the need in the art, consider hypogonadal men, for example. Hypogonadism in man is characterized by a deficiency or absence of endogenous testosterone production.

Abnormally low levels of testosterone may place men at risk of "Andropause", wherein men are at greater risk of cardiovascular disease, Alzheimer's disease, and osteoporosis.

Testosterone has traditionally been used to treat hypogonadal men. However, to be most effective, the treatment must be capable of complete physiologic testosterone replacement. Moreover, the treatment must be capable of providing sustained levels of testosterone through the night, preferably sustaining a peak in the middle of the night. Transdermal testosterone patches typically produce only sub-physiologic levels and thus incomplete relief. Similarly, the prior art buccal tablets hereintofore described would be ineffective or impractical for such sustained testosterone delivery.

The hormone testosterone, like many other drugs, including many other proteins and glycoproteins, undergoes high first pass metabolism. Accordingly, as will be appreciated by one of ordinary skill in the art, buccal or vaginal tablets consisting of materials that are incapable of keeping the interior reservoir of the tablet in the dry state for prolonged periods are inherently incapable of preventing dissolution and swallowing or dissolution and rapid absorption through the mucosa of the active ingredient. Furthermore, as will be appreciated by one of ordinary skill in the art, tablets which are unable to quickly adhere to the target area or are able to become dislodged are impractical for treatments which use night-time delivery, such as testosterone treatment.

Furthermore, as will be appreciated by one of ordinary skill in the art, the advantages of a sustained release, bioadhesive tablet according to the present invention are not limited to the treatment of hypogonadism in men. For example, patients often require sustained release hormone treatment for various conditions. In addition, other medications, such as steroids for treating such conditions as asthma, involve treatments where desired peak levels are at night

during sleep-time hours. Accordingly, one of ordinary skill in the art will appreciate that there exists a long-felt, yet unresolved, need to develop a bioadhesive, sustained release tablet to overcome the aforementioned needs of the art, including, but not limited to, the delivery of therapeutically effective amounts of an active ingredient which may be metabolized or otherwise degraded by moisture, enzymes, or pH effects, such as glycoproteins, proteins, sex hormones, anti-hormones, nitrates, beta-agonists, beta-antagonists, opioids, opioid-antagonists antidepressants, HMG CoA reductase inhibitors, antihistamines, ACE inhibitors, and/or prostaglandins.

SUMMARY OF THE INVENTION

The present invention meets the aforementioned needs in the art. Accordingly, it is an object of the invention to provide a bioadhesive tablet that adheres immediately or almost immediately to the target tissue area of a body cavity and generally stays attached substantially throughout treatment. In accordance, with this aspect of the invention, there is provided a bioadhesive tablet that can stay attached and deliver active ingredients in the buccal cavity for as much as eighteen hours or more. In accordance with a related aspect of the invention, there is provided a bioadhesive tablet that can stay attached and deliver active ingredients vaginally for as much as 72 hours or more.

It is another object of the invention to provide a bioadhesive tablet that progressively hydrates, whereby the inner core of the tablet remains protected from moisture and the surrounding environment. In accordance with this aspect of the invention there is provided a bioadhesive tablet suitable for sustained release use in mucosal and other body cavities even with

active ingredients comprising proteins or glycoproteins or other treating agents that are particularly susceptible to metabolism, or to enzymatic, pH, or moisture-induced degradation.

It is a related object of the invention to provide a bioadhesive tablet having both controlled and sustained release properties due to a tablet formulation wherein the active ingredient is only progressively made bioavailable over an extended time period by the progressive hydration of the tablet's dry reservoir of active ingredient.

It is another object of the invention to provide a bioadhesive tablet according to the invention that also gelifies and/or swells to help protect a patient using the tablet buccally from asphyxiation, particularly a sleeping patient undergoing treatment.

It is yet another object of the invention to provide methods of making bioadhesive tablets in accordance with the aforementioned objects of the invention. In accordance with one aspect of the invention, there is provided a method of making bioadhesive tablets wherein an active ingredient resistant to premature metabolism and/or degradation is added in the first and/or second step (manufacture of granulate). In accordance with a related aspect of the invention there is provided a method of making bioadhesive tablets wherein an active ingredient prone to premature metabolism and/or degradation is added in the second step (manufacture of the tableting mixture) after the granulate is dried and sieved. Of course, other concerns or factors may affect the choice of which step or steps are appropriate for adding a particular active ingredient.

It is yet another object of the invention to provide methods of using bioadhesive tablets as described herein. In accordance with one aspect of the invention, there is provided a method of using a bioadhesive tablet to administer to a male patient a sustained release of testosterone. In accordance with a related aspect of the invention, there is provided a method of using a

bioadhesive tablet to administer to a female patient a sustained release of a hormone, such as testosterone.

The inventors of the present invention have discovered, quite unexpectedly, that these and other objects for the invention may be achieved by making and using tablets comprising an active ingredient, water soluble polymers (e.g., CARBOPOL™ 974P), and insoluble polycarbophil (e.g., NOVEON®, available from B.F. Goodrich Specialty Polymers of Cleveland, OH), and preferably hydroxypropylmethyl cellulose (HPMC), lactose, corn starch and other standard tablets ingredients, such as magnesium stearate and talc.

Bioadhesive, progressive hydration tablets according to the invention may be used with any suitable active ingredient and may be used to deliver a therapeutic amount of the active ingredient to a patient at controlled rates for sustained periods of time. Tablets according to the invention may also be constructed in any suitable shape and any suitable size consistent with the intended therapeutic use of the tablet.

Tablets according to the invention may comprise any suitable amount of active ingredient. Suitable amounts of active ingredient according to the invention are may be from minuscule amounts of active ingredient to about 50%, or more, by weight active ingredient. As will be appreciated by one of ordinary skill in the art, "minuscule amounts" is intended to cover those amounts of active ingredient that are disproportionately small relative to the tablet, for example, when only a few micrograms of active ingredient are to be delivered via a tablet weighing over a hundred milligrams. Accordingly, one of ordinary skill in the art will appreciate that any amount of active ingredient, in any ratio, is within the scope of the present invention.

The balance of the tablet according to the invention may comprise water soluble polymer(s) and water insoluble cross-linked polycarboxylic polymer(s). Also, according to the invention, exemplary tablets preferably have between about 1% and about 75% by weight water soluble polymer and between about .5% and about 10% by weight water insoluble cross-linked polycarboxylic polymer. In accordance with the invention, such exemplary tablets also preferably include between about 5% and about 50% cellulose. Also in accordance with the invention, presently preferred tablets may have between about .5% and about 25% by weight starch. These preferred tablets may also have between about 1% and about 50% by weight lactose.

Furthermore, according to the invention, preferred tablets may comprise from about .01% up to about 2% silica; and/or up to about .5% by weight talc; and/or up to about 2.5% by weight magnesium stearate.

Accordingly, one of ordinary skill in the art will appreciate that the components of the tablets can be varied to suit a particular purpose. For example, the inventors of the present invention have discovered, quite unexpectedly, that one way of increasing (decreasing) the time it takes a progressive hydration tablet to hydrate is by decreasing (increasing) the amount of lactose and/or starch and increasing (decreasing) the amount of water soluble polymer. Alternatively, the density of the tablet may be altered to affect the hydration period.

Active ingredients suitable for use in the present invention include any active ingredient or ingredients requiring sustained or controlled release, any active ingredient or ingredients requiring extended protection from premature degradation of the active by moisture, pH effects, or enzymes, or any active ingredient requiring administration to a patient with protection from first-pass hepatic metabolism. Exemplary active ingredients suitable for use with the present

invention include, but are by no means limited to: (1) glycoproteins, such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (HCG), thyroid-stimulating hormone (TSH), and the like; (2) proteins, such as GnRH (agonist and antagonist), oxytocin analogs, somatostatin analogs, tissue plasminogen activator (TPA), growth hormone releasing hormone (GHRH), corticotropin-releasing hormone analogs (CRH analogs), and the like; (3) sex hormones, such as estradiol, testosterone, progesterone, and the like; (4) anti-hormones, such as tamoxifen, mifepristone, and the like; (5) nitrates, such as nitroglycerin, isosorbide, erythrityl tetranitrate, pentaerythritol tetranitrate, and the like; (6) beta-agonists, such as terbutaline, albuterol, pirbuterol, bitolterol, ritodrine, and the like; (7) beta-antagonists, such as propranolol, metoprolol, nadolol, atenolol, timolol, esmolol, pindolol, acebutolol, labetalol, and the like; (8) opioids, such as morphine, hydromorphone, oxymorphone, codeine, hydrocodone, oxycodone, levorphanol, levallorphan, buprenorphine, fentanyl, nalbuphine, butorphanol, pentazocine, and the like; (9) opioids-antagonists, such as naloxone, nalmeferene, and the like; (10) antidepressants, such as amitriptyline, amoxapine, desipramine, doxepin, imipramine, maprotilen, nortriptyline, protriptyline, trimipramine, fluoxetine, trazodone, and the like; (11) HMG CoA reductase inhibitors, such as lovastatin, mevastatin, simvastatin, pravastatin, atorvastatin, and the like; (12) antihistamines, such as loratadine, chlorpheniramine maleate, brompheniramine maleate, diphenhydramine, dimenhydrinate, carbinoxamine, promethazine, triprolidine, and the like; (13) ACE inhibitors, such as captopril, enalapril, lisinopril, and the like; and, (14) prostaglandins, such as misoprostol and the like. Accordingly, one of ordinary skill in the art will appreciate that tablets according to the invention may be used with a wide variety of active ingredients to treat a wide variety of conditions.

The aforementioned and other aspects of the invention will become more clear by reference to the Figures and descriptions of preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a series of photographs depicting the progressive hydration of a
5 bioadhesive tablet according to the invention.

Figure 2 is a flowchart depicting a presently preferred method of making bioadhesive tablets according to the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

A presently preferred embodiment of the invention is depicted in Figure 1. As shown
10 in the first-frame of Figure 1, before the tablet is administered all of the active is in the dry state and thus, not subject to the deleterious action of moisture, pH effects, enzymes or other chemicals. It is also not available for absorption (bioavailable). As shown in frames 2-6 of Figure 1, over time the residual portion of the active remains in the dry state which both protects it from water and the immediate environment as well as allowing it to serve as a
15 reservoir for the sustained and controlled release of the active. Such a delivery system is well suited for the delivery of proteins, glycoproteins, and other drugs which must be protected from metabolism or during prolonged administration from enzymatic, pH, or moisture-induced degradation.

In a preferred embodiment, when used buccally, progressive hydration of the
20 bioadhesive tablet protects the patient, should the tablet become dislodged, by gelifying and becoming heavier and thus less likely to float in the airway, risking aspiration. This makes

this embodiment particularly well suited for agents that should reach their peak levels in the middle of the night, e.g., hormones like testosterone or steroids to treat asthma. According to the invention, the hydration of the tablet can preferably take hours (e.g. 12 to 24 hours) when formulated for buccal tablets or even days when formulated for vaginal use. As will be

5 appreciated by one of ordinary skill in the art, prior art bioadhesive tablets do not protect the active ingredient from moisture, pH, or from enzymes produced by bacteria in the septic oral and vaginal orifices.

Furthermore, as will be appreciated by one of ordinary skill in the art following the teaching of the present application, the tablet can be sized shaped and dosed to meet the needs

10 of the particular treatment being undertaken. For example, the buccal bioadhesive tablet depicted in Figure 1 was constructed to be only 9mm in diameter for the comfort of the patient, but made capable of delivering 7mg of testosterone per day, full physiologic level. By contrast, prior art transdermal patches were only capable of delivering 5mg per day, in other words a sub-physiologic level.

15 A presently preferred method of manufacturing bioadhesive tablets is diagramed in Figure 2. The presently preferred method involves three steps as described below:

1. First step: manufacture of the granulate.

Hydroxypropylmethyl cellulose 15 000(=HPMC 15 000) is mixed with corn starch and lactose and in case of an active ingredient non sensitive to moisture the active is added.

20 The mixture is wet with an aqueous solution of hydroxypropylmethyl cellulose 5 (=HPMC 5) and knead/granulated.

The granulate is dried in an oven under warm air (50°C) until moisture content is less than 2.5%

The dried granulate is broken with a stainless steel sieve oscillating granulator mesh size 1000 μm .

- 5 2. Second step: manufacture of the tableting mixture. Talc, silicon dioxide magnesium stearate, and in a case of an active sensitive to moisture, the active ingredient is added. All is sieved through a sieving machine having aperture size 500 μm and then transferred into a free-fall mixer.

 Addition of the granulate of step 1, followed by polycarbophil, carbomer and lactose.
10 The whole is mixed until homogenous.

3. Third step: tableting

The tableting mixture is compressed into tablets by means of a rotative tableting machine equipped with punches 9mm flat on the upper side and curved ($r=9\text{mm}$) on the lower side both with beveled edge. The tablets are dedusted and packed.

15 As depicted in Figure 2, an active ingredient that is non-sensitive to moisture is preferably added during the manufacture of the granulate. However, alternatively, the active ingredient can be added during the second step after the granulate is dried and sieved. Also, as will be appreciated by one of ordinary skill in the art, this second method is particularly preferred when the active ingredient is sensitive to moisture.

20 In a presently preferred manufacturing process, the active ingredient is preferably protected from moisture. A wet granulation is made of lactose, corn starch and HPMC.

Testosterone, polycarbophil, carbomer 934P, talc and magnesium stearate are added dry for the final compression.

Furthermore, as will be appreciated by one of ordinary skill in the art following the teaching of the present application, the materials of construction can be varied to optimize the desired characteristics of the tablet. For example, the present inventors have discovered that, quite unexpectedly, by progressively decreasing the amount of lactose and corn starch and progressively increasing the amount of carbomer 934P, the amount of time it takes a tablet to hydrate is progressively increased. Accordingly, as will be appreciated by one of ordinary skill in the art, tablets suited for specific treatments (i.e., specific active, specific dose, specific delivery time) can be manufactured.

These and other aspects of the invention may be more clearly shown by way of example.

EXAMPLE: TESTOSTERONE TABLET

The following is an example of a formulation (Formulation 8, batch #00029906) designed for complete physiologic replacement of testosterone in men:

Testosterone	30.000 mg	24.0%
HPMC	26.250 mg	21.0%
Corn Starch	22.500 mg	18.0%
Monohydrated Lactose	30.125 mg	24.1%
Silica	1.250 mg	1.0%
Polycarbophil (Noveon)	3.125 mg	2.5%
Carbomer 974P	9.375 mg	7.5%

Talc	1.500 mg	1.2%
Magnesium stearate	0.875 mg	0.7%

Formulations like the one above produced sustained release in in-vitro dissolution tests. When used in female subjects formulas like this one also produce a sustained and controlled release of testosterone for 12 hours or more.

Table 1 depicts nine different formulations of bioadhesive tablets according to the invention. The active ingredient, testosterone, was held constant at 30.0 mg (24% by weight) so the effect of varying the proportions of the inactive ingredients could be studied.

The testosterone dissolution rates of selected formulations were then studied. Table 2 depicts the testosterone dissolution rate of six tablets selected from Formula 1, batch #0069904. Table 3 depicts the testosterone dissolution rate of six tablets selected from Formula 3, batch #0049904. Table 4 depicts the testosterone dissolution rate of six tablets selected from Formula 5, batch #0029904. Table 5 depicts the testosterone dissolution rate of Formula 6, batch #0019904.

The dissolution rate data was then graphed to illustrate the percent of testosterone released per hour. Chart 1 depicts the testosterone release rate for Formula 1 (see Table 2). Chart 2 depicts the testosterone release rate for Formula 3 (see Table 3). Chart 3 depicts the testosterone release rate for Formula 5 (see Table 4). Chart 4 depicts the testosterone release rate for Formula 6 (see Table 5).

As shown in the charts and tables, by decreasing the amount of lactose and corn starch and increasing the amount of carbomer 934P, the time it takes for the tablet to hydrate is progressively increased. Formulation 1 (0069904) and others like it with high levels of carbomer 934P and low levels of lactose and corn starch are probably best suited for vaginal administration where release is often required over a period days. In the first example given above Formulation 8 (0029906), where the levels of lactose and corn starch are high and carbomer 934P is low, the formula is probably better suited to buccal administration where 12 hours of delivery is usually sufficient.

As will be appreciated by one of ordinary skill in the art, the examples and preferred embodiments are not intended to be limiting, and the invention applies to tablets comprised of any active ingredient and any combination of tablet materials. Furthermore, as will be appreciated by one of ordinary skill in the art, the invention is intended to cover the methods of manufacturing and therapeutic uses of the aforementioned tablets.

Testosterone KI

Batch #	Form. 1		Form. 2		Form. 3		Form. 4		Form. 5		Form. 6		Form. 7		Form. 8		Form. 9	
	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%
Testosterone	30.000	24.00	30.000	24.00	30.000	24.00	30.000	24.00	30.000	24.00	30.000	24.00	30.000	24.00	30.000	24.00	30.000	24.00
HPMC 90SH-15000	31.250	25.00	30.000	24.00	28.750	23.00	27.500	22.00	26.250	21.00	26.250	21.00	26.250	21.00	26.250	21.00	26.250	21.00
Corn starch	2.500	2.00	7.500	6.00	12.500	10.00	17.500	14.00	22.500	18.00	22.500	18.00	22.500	18.00	22.500	18.00	22.500	18.00
Monohydrated lactose	11.375	9.10	13.875	11.10	16.375	13.10	18.875	15.10	21.375	17.10	24.500	19.60	27.625	22.10	30.125	24.10	33.250	26.60
Silica	1.250	1.00	1.250	1.00	1.250	1.00	1.250	1.00	1.250	1.00	1.250	1.00	1.250	1.00	1.250	1.00	1.250	1.00
Polycarbophil acid (Noveon AA.)	3.125	2.50	3.125	2.50	3.125	2.50	3.125	2.50	3.125	2.50	3.125	2.50	3.125	2.50	3.125	2.50	3.125	2.50
Carbomer 974 R	43.750	35.00	37.500	30.00	31.250	25.00	25.000	20.00	18.750	15.00	15.625	12.50	12.500	10.00	9.375	7.50	6.250	5.00
Talc	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	1.500	1.20	1.500	1.20
Magnesium stearate	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70
Total weight	125.000	100.000	125.000	100.000	125.000	100.000	125.000	100.000	125.000	100.000	125.000	100.000	125.000	100.000	125.000	100.000	125.000	100.000

* Hydroxypropylmethyl cellulose

TABLE 1

TESTOSTERONE DISSOLUTION RATE

BATCH: 0069004 (Formula 1)
DISSOLUTION APPARATUS: ROTATING PADDLE 60 RPM / PLATINUM WIRE SPHERAL

SAMPLE	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)
	0	1	2	4	6	8	14
1	0.0	0.7	1.9	7.8	10.6	16.0	80.6
2	0.0	0.6	1.7	6.7	11.7	18.9	88.3
3	0.0	0.7	2.0	6.9	11.7	17.9	84.9
4	0.0	0.6	1.7	7.0	11.2	17.1	88.3
5	0.0	0.7	1.9	6.8	10.9	17.8	87.4
6	0.0	0.7	2.1	6.6	12.4	18.3	86.0
AVERAGE VALUE	0.0	0.7	1.9	6.9	11.4	17.4	86.6

TABLE 2

TESTOSTERONE DISSOLUTION RATE

DATE: 04/04/04
 DISSOLUTION APPARATUS: ROTATING PADDLES 60 RPM / PLATINUM WIRE SPECIAL

(For Table 3)

SAMPLE	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)
	0	1	2	4	6	8	24
1	0.0	0.9	3.1	5.6	10.6	16.1	43.6
2	0.0	1.1	3.1	5.6	10.3	16.9	42.2
3	0.0	1.2	3.4	6.3	11.8	18.0	43.4
4	0.0	0.9	2.9	5.4	10.8	16.7	42.7
5	0.0	1.1	3.1	5.7	10.4	16.2	43.0
6	0.0	1.0	2.9	5.6	11.0	16.8	43.6
AVERAGE VALUE	0.0	1.0	3.0	5.7	10.9	16.9	43.4

TABLE 3

TIBOSTERONE DISSOLUTION RATE

BATCH: 02M04
 DISSOLUTION APPARATUS: ROTATING PADDLE 60 RPM / PLATINUM WIRE SPHERAL

SAMPLE	WITHDRAW (HOUR)	1	2	4	6	8	14
1	0.0	0.9	2.2	5.9	10.5	16.3	80.3
2	0.0	0.9	2.5	6.7	11.8	17.8	87.5
3	0.0	0.9	3.4	6.9	12.3	17.7	75.2
4	0.0	0.9	2.3	6.8	12.4	18.6	87.4
5	0.0	0.9	2.5	6.9	12.9	19.5	80.2
6	0.0	0.9	2.7	6.8	12.3	18.5	80.0
AVERAGE VALUE	0.0	0.9	2.4	6.5	12.4	18.1	81.5

TABLE 4

TESTOSTERONE DISSOLUTION RATE

BATCH: 0019904
 DISSOLUTION APPARATUS: ROTATING PADDLE 60 RPM / PLATINUM WIRE SPHERAL

(Formula 6)

SAMPLE	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)
	0	1	2	4	6	8	24
1	0.0	1.2	2.1	3.9	11.1	16.1	71.7
2	0.0	0.8	2.0	5.0	9.7	14.1	70.1
3	0.0	0.9	2.3	6.4	11.3	15.8	74.6
4	0.0	0.9	2.0	5.5	10.4	15.0	68.6
5	0.0	0.8	1.8	4.9	9.9	14.6	76.6
6	0.0	0.9	1.8	4.9	9.9	14.6	76.6
AVERAGE VALUE	0.0	0.9	2.0	5.4	10.3	14.8	72.0

TABLE 5

% of Testosterone Released (dissolution / rotating paddle 60 rpm + platinum wire spiral)
single value (n=6), Batch 0069904 (Formula 1)

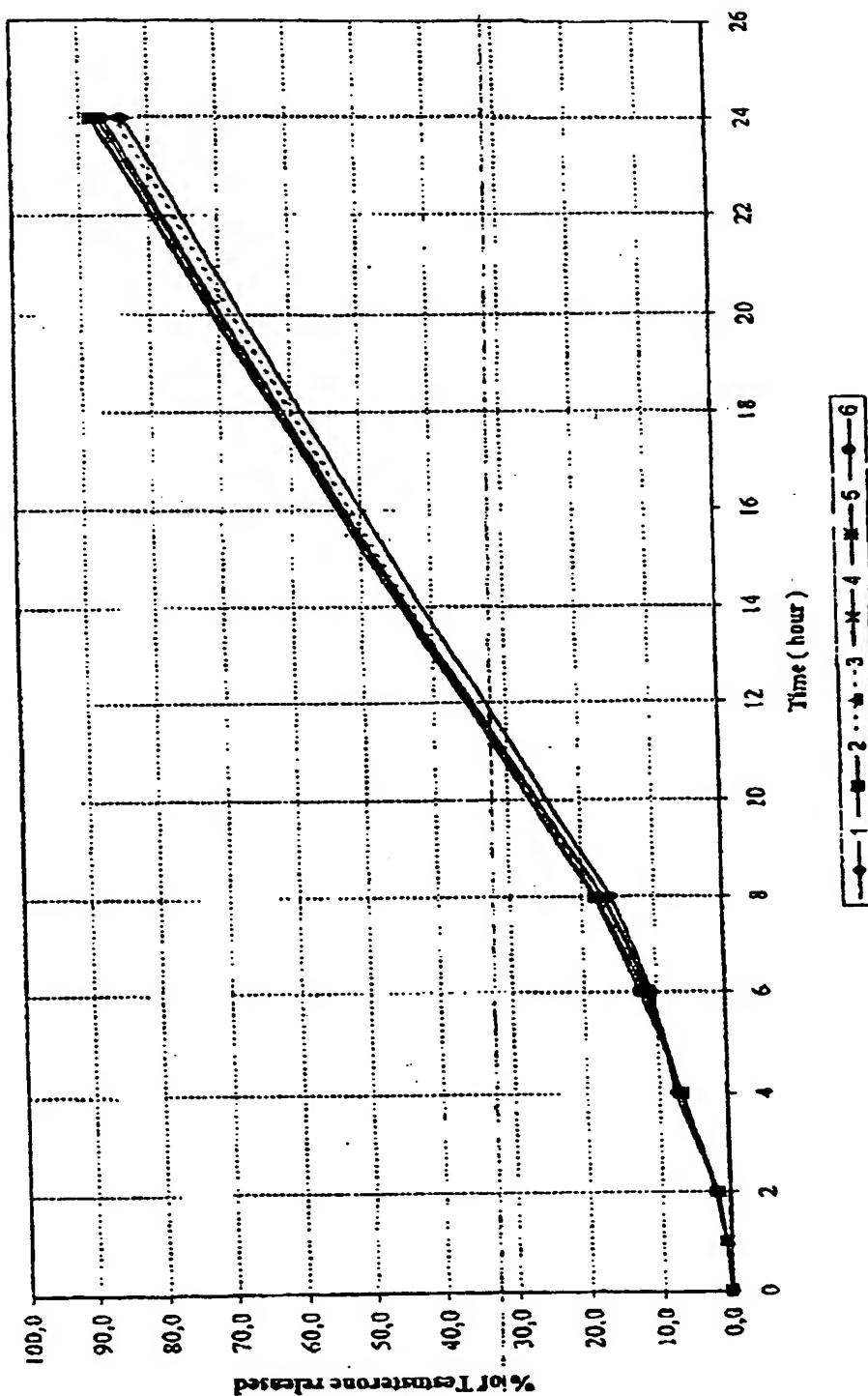


CHART 1

% of Testosterone released (dissolution / rotating paddle 60 rpm + platinum wire spiral)
single value (n=6), Batch 0049904 (Formula 3)

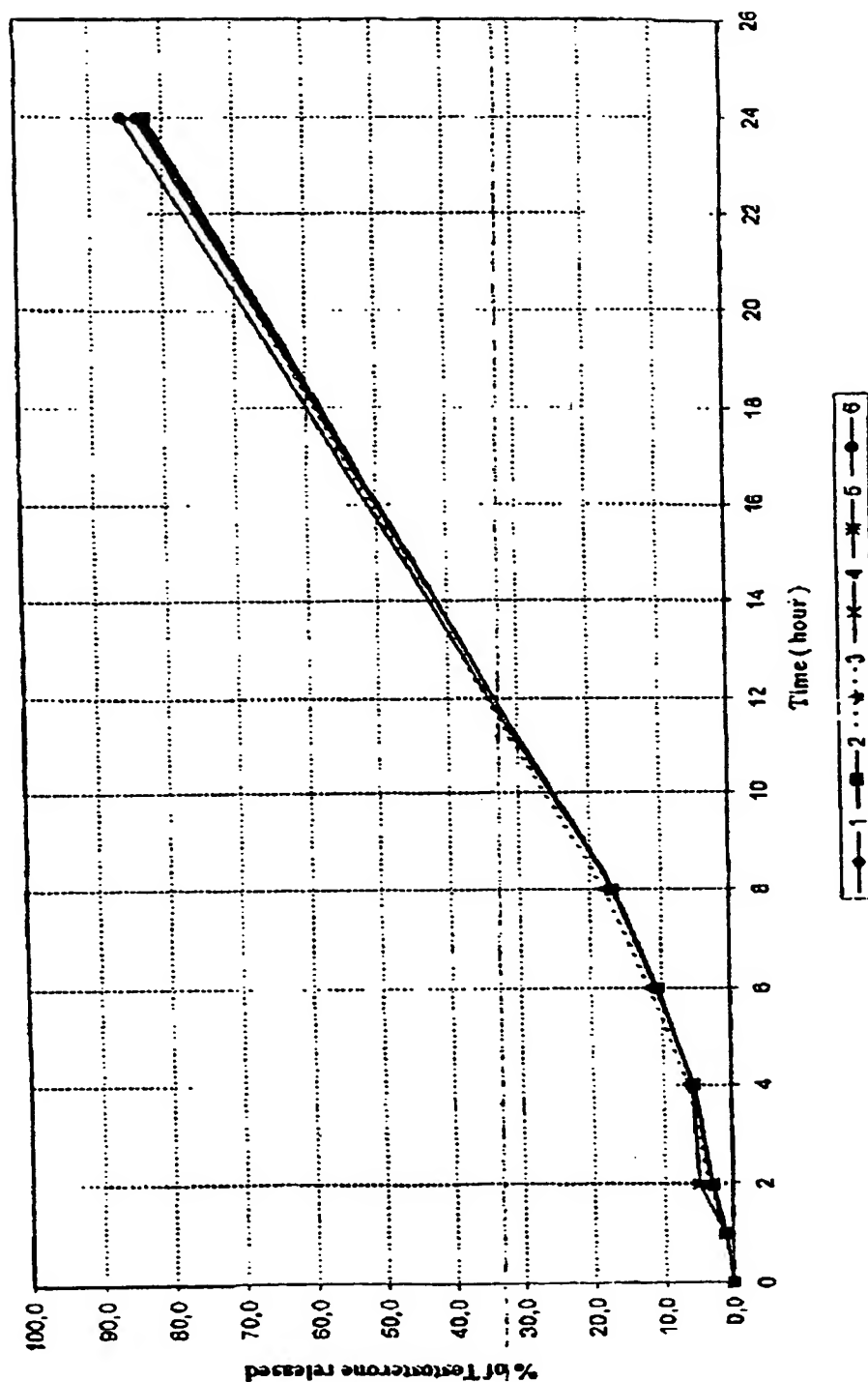
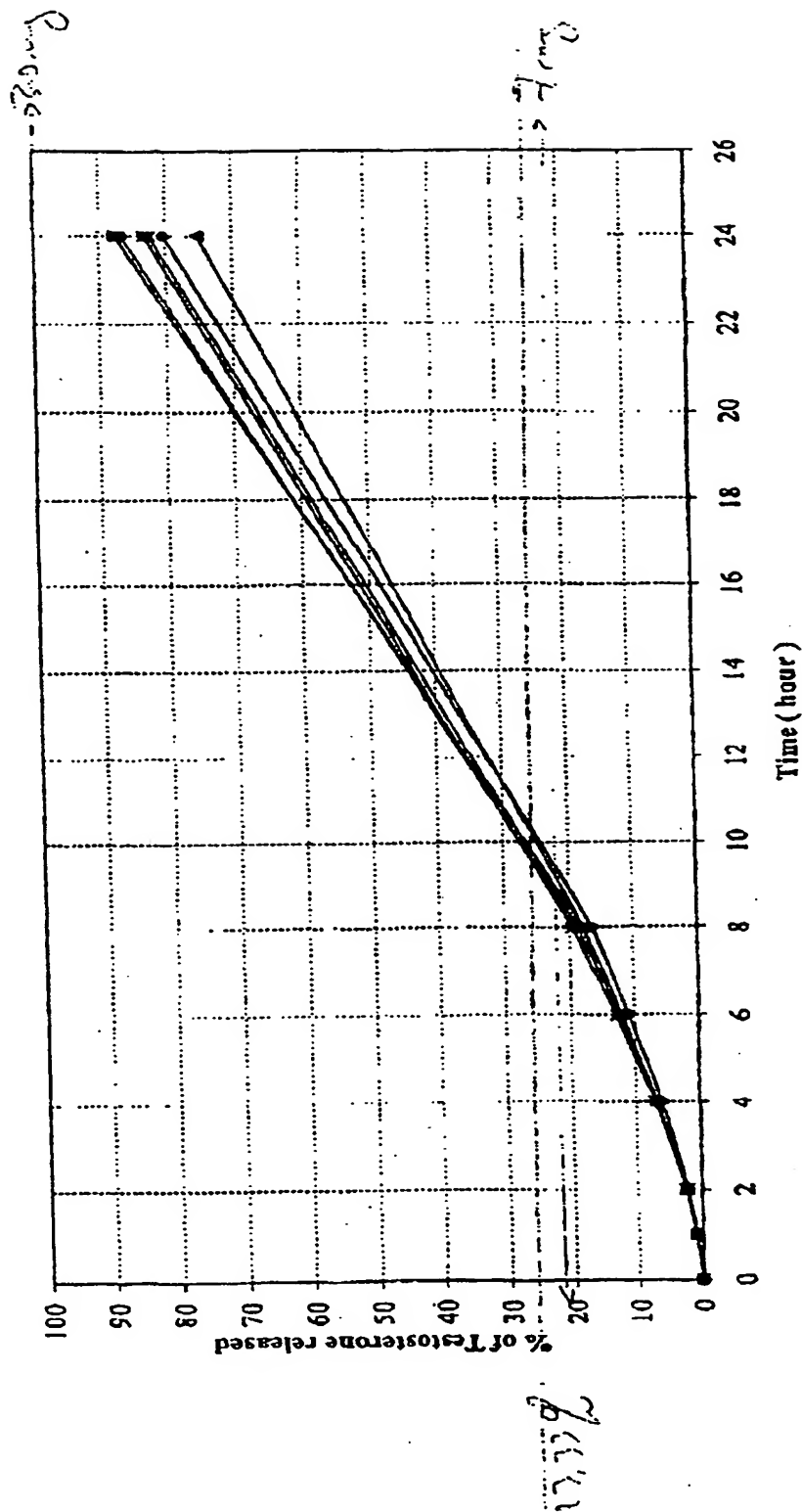


CHART 2

% of Testosterone released (dissolution / rotating paddle 60 rpm + platinum wire spiral)
single value (n=6), Batch 0029904 (Fresenius)



1 —●— 2 —●— 3 —●— 4 —●— 5 —●— 6 —●—

CHART 3

% of Testosterone released (dissolution / rotating paddle 60 rpm + platinum wire spiral)
single value (n=6), Batch 0019904 (Formulation 6)

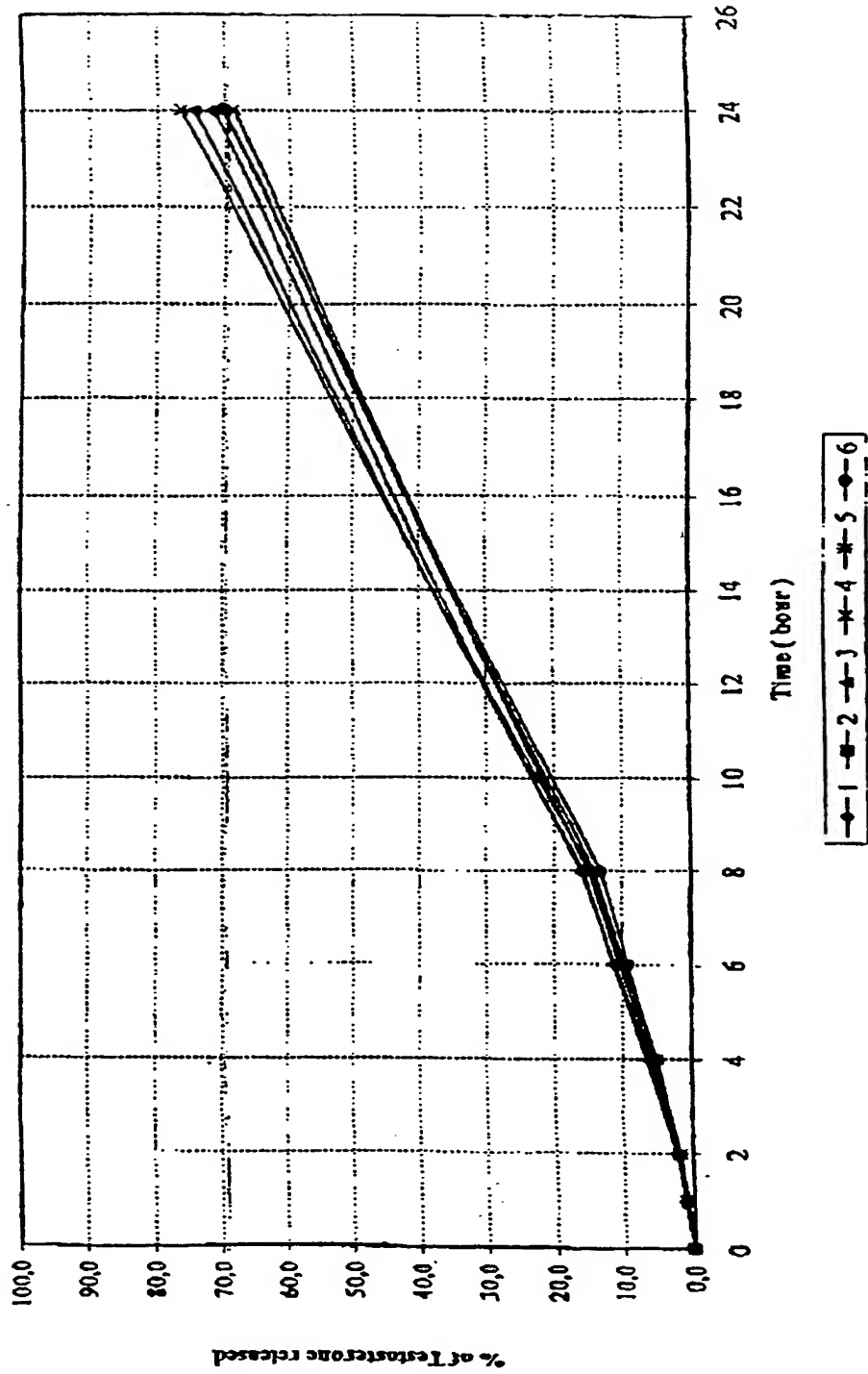


CHART 21

WHAT IS CLAIMED IS:

1. A sustained release, progressive hydration bioadhesive tablet comprising:
an effective amount of active ingredient,
about 5% to about 50% by weight cellulose,
about .5% to about 25% by weight starch,
about 1% to about 50% by weight lactose,
about .5% to about 10% by weight water insoluble cross-linked polycarboxylic polymer, and
about 1% to about 75% by weight water soluble polymer.
2. The tablet of claim 1, wherein said tablet comprises between a minuscule amount and about 50% by weight active ingredient.
3. The tablet of claim 2, further comprising:
about 1% by weight silica.
4. The tablet of claim 3, further comprising:
about .5% to about 2% by weight talc.
5. The tablet of claim 4, further comprising:
about .5% to about 1% by weight magnesium stearate.
6. The tablet of claim 1 or 5, wherein said active ingredient is selected from the group consisting of glycoproteins, proteins, sex hormones, anti-hormones, nitrates, beta-agonists, beta-antagonists, opioids, opioid-antagonists, antidepressants, HMG CoA reductase inhibitors, antihistamines, ACE inhibitors, prostaglandins, and any other active ingredient which is metabolized or degraded by moisture, enzymes or pH.

7. The tablet of claim 5, wherein said starch is present in about 2% to about 10% by weight, said lactose is present in about 8% to 16% by weight, and said water soluble polymer is present in about 25% to about 35% by weight, and wherein said tablet is adapted for delivering said active ingredient to the bloodstream of a patient via the patient's vaginal cavity.
8. The tablet of claim 5, wherein said starch is present in about 14% to 24% by weight, said lactose is present in about 17% to 27% by weight, and said water soluble polymer is present in about 5% to about 20% by weight, and wherein said tablet is adapted for delivering said active ingredient to the bloodstream of a patient via the patient's buccal cavity.
9. A sustained release, progressive hydration bioadhesive tablet comprising:
an effective amount of an active ingredient,
about 2% to about 30% by weight binder,
about 5% to about 40% by weight lactose,
about 1% to about 3% by weight water insoluble cross-linked polycarboxylic polymer, and
about 5% to about 50% by weight water soluble polymer.
10. The buccal tablet of claim 9, further comprising:
about .2 to 2% by weight silica.
11. The buccal tablet of claim 10, further comprising:
about .5% to about 2% by weight talc.
12. The tablet of claim 11, further comprising:
about .5% to about 2% by weight magnesium stearate.

13. The buccal tablet of claim 11, wherein said active ingredient is testosterone and said testosterone is present in an amount of about 1% to about 30% by weight.
14. The tablet of claim 13, wherein said starch is present in about 2% to about 10% by weight, said lactose is present in about 8% to 16% by weight, and said water soluble polymer is present in about 25% to about 35% by weight, and wherein said tablet is adapted for delivering said active ingredient to the bloodstream of a patient via the patient's vaginal cavity.
15. The tablet of claim 13, wherein said starch is present in about 14% to 24% by weight, said lactose is present in about 17% to 27% by weight, and said water soluble polymer is present in about 5% to about 20% by weight, and wherein said tablet is adapted for delivering said active ingredient to the bloodstream of a patient via the patient's buccal cavity.
16. A method of delivering an active ingredient to a person comprising sustained release administration of an active ingredient via a progressive hydration bioadhesive tablet.
17. The method of claim 16 wherein the bioadhesive tablet comprises a water insoluble but water-swellaable cross-linked polycarboxylic polymer, a water soluble polymer and testosterone.
18. A method of treating or preventing ischemia or Alzheimer's disease comprising administering to a patient a therapeutically effective amount of testosterone via a sustained release, progressive hydration bioadhesive tablet.
19. The method of claim 18 wherein the bioadhesive tablet is a buccal tablet comprising a water insoluble cross-linked polycarboxylic polymer, a water soluble polymer and testosterone.

20. The method of claim 18, wherein the bioadhesive tablet is a vaginal tablet comprising a water insoluble cross-linked polycarboxylic polymer, a water soluble polymer and testosterone.
21. A sustained release, progressive hydration bioadhesive tablet for delivering an active ingredient to the bloodstream of a patient to treat a health condition, comprising a therapeutically effective amount of an active ingredient, a water insoluble cross-linked polycarboxylic polymer, and a water soluble polymer.
22. Use of an active ingredient together with a water insoluble cross-linked polycarboxylic polymer and a water soluble polymer for the preparation of a sustained release, progressive hydration bioadhesive tablet for delivering an active ingredient to the bloodstream of a patient to treat a health condition.

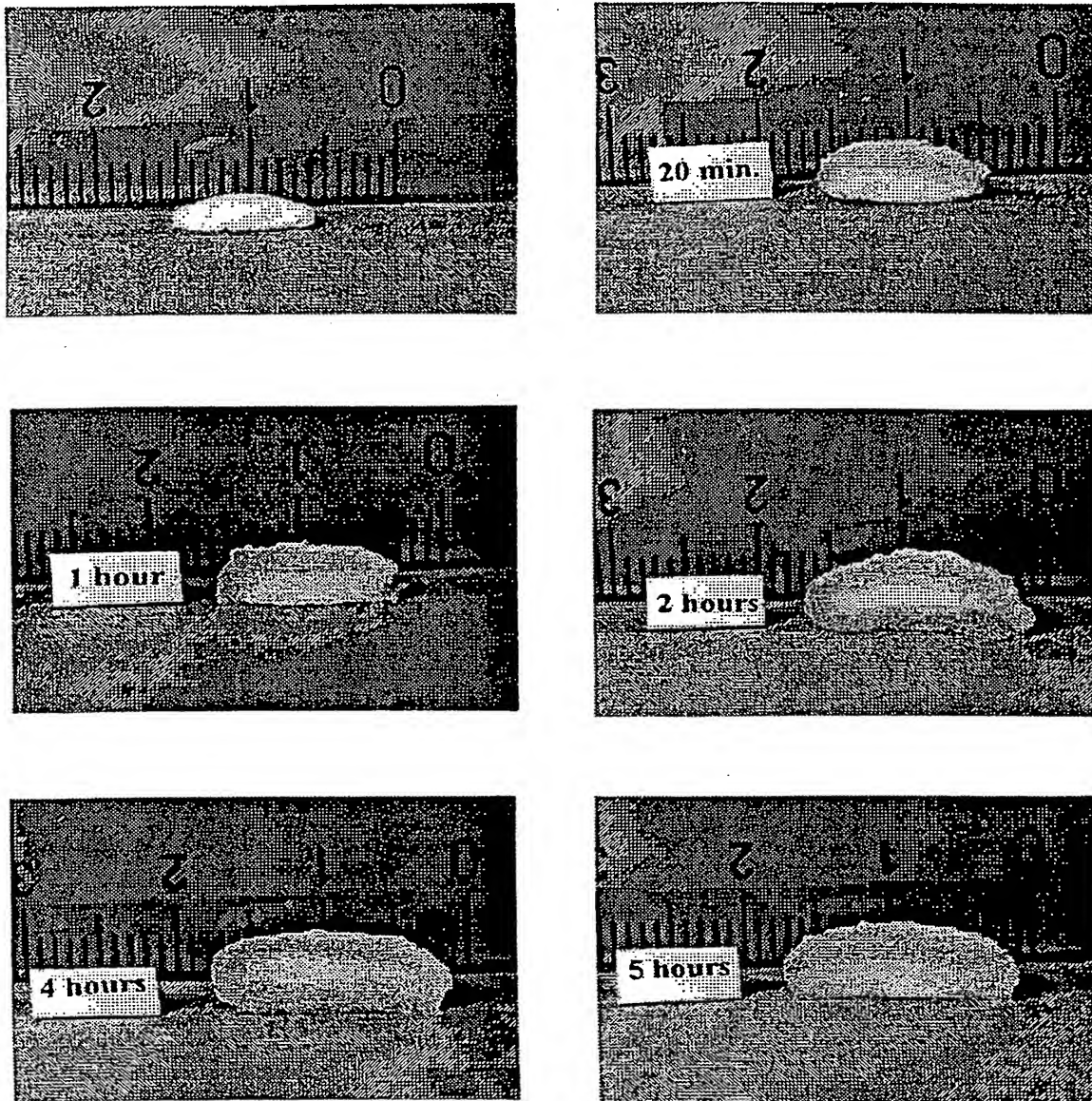
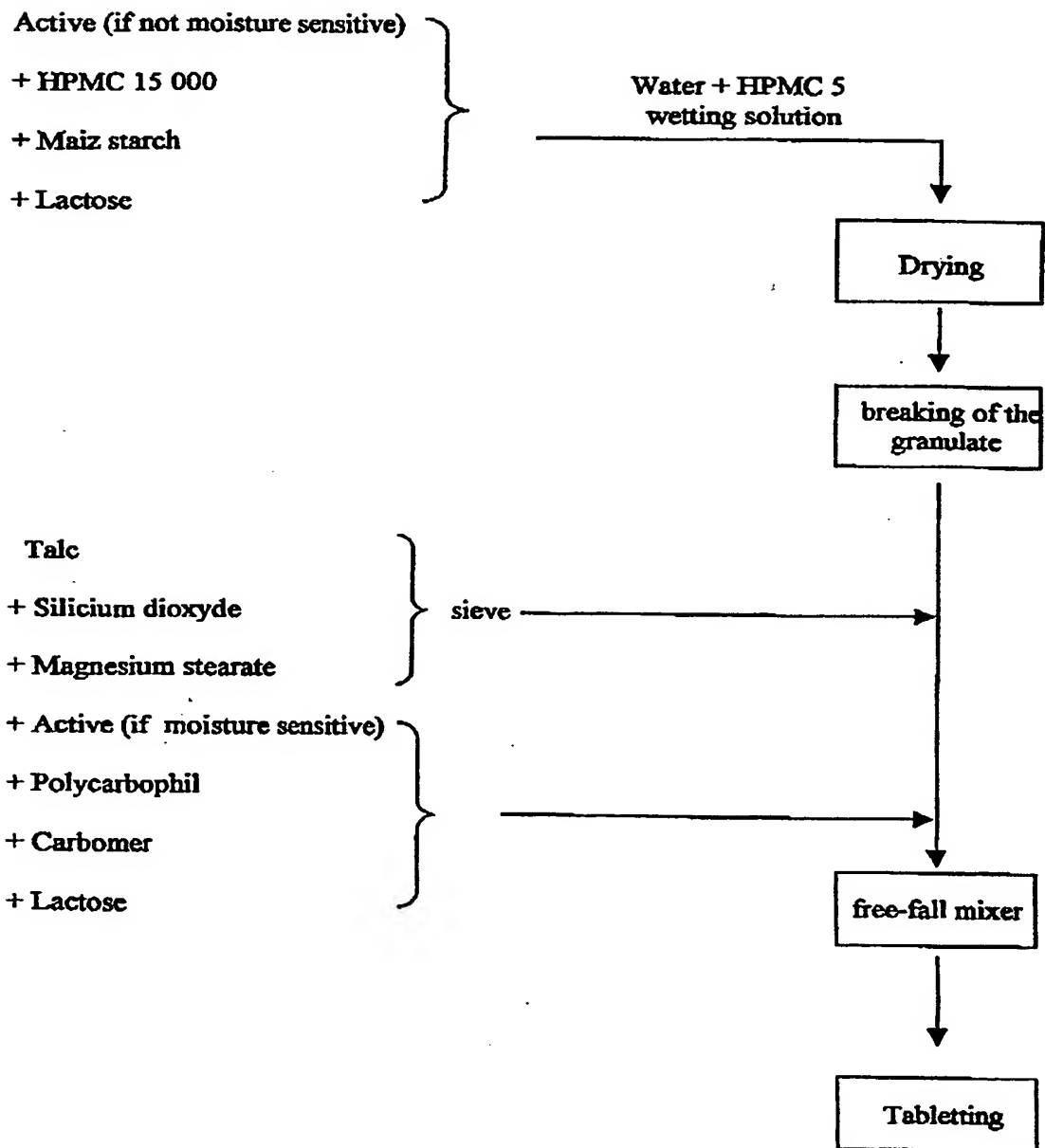
BIOADHESIVE PROGRESSIVE HYDRATION TABLET

FIG 1



F162

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 99/19260

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VOORSPOELS J ET AL: "BUCCAL ABSORPTION OF TESTOSTERONE AND ITS ESTERS USING A BIOADHESIVE TABLET IN DOGS" PHARMACEUTICAL RESEARCH, US, NEW YORK, NY, vol. 13, no. 8, August 1996 (1996-08), pages 1228-1232, XP000865566 ISSN: 0724-8741 page 1228	16-19
X A	EP 0 159 604 A (TOYO BOSEKI) 30 October 1985 (1985-10-30) page 33 -page 36	16 1-15, 17-19
X A	EP 0 654 261 A (VETOQUINOL SA) 24 May 1995 (1995-05-24) page 4; example 1	16 1-15, 17-19

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

3 February 2000

Date of mailing of the international search report

10/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Boulois, D

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/19260

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 226 848 A (MACHIDA YOSHIHARU ET AL) 7 October 1980 (1980-10-07) column 7, line 44 - line 63 claims -----	16
A	EP 0 488 139 A (HOKURIKU PHARMACEUTICAL) 3 June 1992 (1992-06-03) page 7; example 18 -----	1-18
A	PATENT ABSTRACTS OF JAPAN vol. 018, no. 371 (C-1224), 13 July 1994 (1994-07-13) & JP 06 100466 A (TSUMURA & CO), 12 April 1994 (1994-04-12) abstract -----	18, 19

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 19260

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 16-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/19260

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0159604	A	30-10-1985	JP 1832298 C	29-03-1994
			JP 5030808 B	11-05-1993
			JP 60215622 A	29-10-1985
			JP 1504244 C	28-06-1989
			JP 60248609 A	09-12-1985
			JP 63047687 B	26-09-1988
			US 4740365 A	26-04-1988
EP 0654261	A	24-05-1995	FR 2712807 A	02-06-1995
			CA 2136404 A	25-05-1995
			US 5723143 A	03-03-1998
US 4226848	A	07-10-1980	JP 1623175 C	25-10-1991
			JP 2042810 B	26-09-1990
			JP 55118413 A	11-09-1980
			CH 638987 A	31-10-1983
			DE 2908847 A	11-09-1980
			FR 2450610 A	03-10-1980
			GB 2042888 A,B	01-10-1980
			US 4250163 A	10-02-1981
EP 0488139	A	03-06-1992	AT 125447 T	15-08-1995
			CA 2055905 A,C	30-05-1992
			DE 69111574 D	31-08-1995
			DE 69111574 T	18-01-1996
			ES 2077144 T	16-11-1995
			JP 2609022 B	14-05-1997
			JP 5246861 A	24-09-1993
			US 5213806 A	25-05-1993
JP 06100466	A	12-04-1994	NONE	



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ :

A61K 9/20

A1

(11) International Publication Number:

WO 00/10536

(43) International Publication Date:

2 March 2000 (02.03.00)

(21) International Application Number: PCT/US99/19260

(22) International Filing Date: 24 August 1999 (24.08.99)

(30) Priority Data:

60/097,843	25 August 1998 (25.08.98)	US
Not furnished	23 August 1999 (23.08.99)	US

(71) Applicant (for all designated States except US): COLUMBIA LABORATORIES, INC. [US/US]; Suite 400, 2875 North-east 191 Street, Aventura, FL 33180 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BOLOGNA, William, J. [US/FR]; 22, place de General Catroux, F-75017 Paris (FR). LEVINE, Howard, L. [US/US]; 107 Balsam Street, Oceanside, NY 11572 (US). CARTIER, Philippe [FR/FR]; 19 rue du General Foy, F-75008 Paris (FR). DE ZIEGLER, Dominique [FR/FR]; 6, rue de la Source, F-75016 Paris (FR).

(74) Agents: KOCH, Robert, J. et al.; Fulbright & Jaworski L.L.P., 801 Pennsylvania Avenue, N.W., Washington, DC 20004-2604 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.

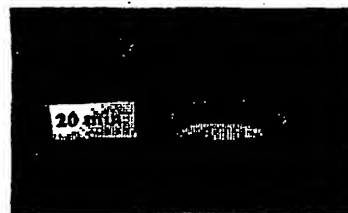
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: EXTENDED RELEASE BUCCAL BIOADHESIVE TABLET

(57) Abstract

A bioadhesive tablet wherein the active ingredient may be protected from water or the surrounding environment, thereby protecting it from metabolism or from other degradation caused by moisture, enzymes, or pH effects, and making it bioavailable only at a controlled rate. The active ingredient may be protected from moisture during the manufacturing process and more importantly may be protected from moisture and the immediate septic environment until after the patient has applied the tablet, and then only at a slow and controlled rate. It is by this process of progressive hydration that the active ingredient remains protected for many hours after administration. It is also by the process of progressive hydration that controlled and sustained release is achieved because only that part of the active ingredient that is the hydrated (aqueous) fraction of the tablet is available for absorption (bioavailable).

BIOADHESIVE PROGRESSIVE HYDRATION TABLET



*(Referred to in PCT Gazette No. 24/2000, Section II)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		



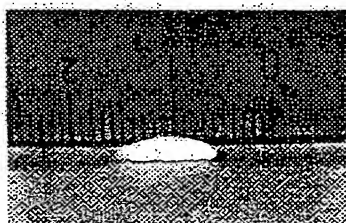
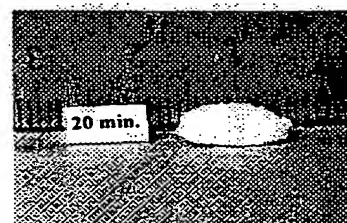
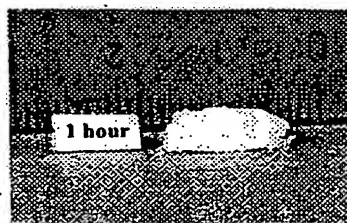
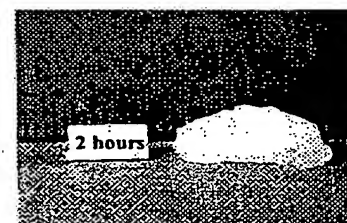
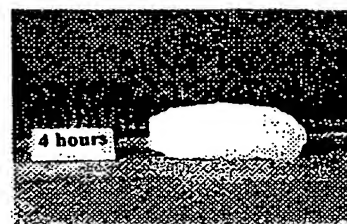
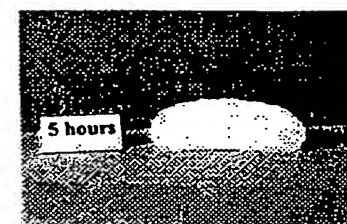
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 9/20	A1	(11) International Publication Number: WO 00/10536 (43) International Publication Date: 2 March 2000 (02.03.00)
<p>(21) International Application Number: PCT/US99/19260</p> <p>(22) International Filing Date: 24 August 1999 (24.08.99)</p> <p>(30) Priority Data: 60/097,843 25 August 1998 (25.08.98) US Not furnished 23 August 1999 (23.08.99) US</p> <p>(71) Applicant (for all designated States except US): COLUMBIA LABORATORIES, INC. [US/US]; Suite 400, 2875 North-east 191 Street, Aventura, FL 33180 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): BOLOGNA, William, J. [US/FR]; 22, place de General Catroux, F-75017 Paris (FR). LEVINE, Howard, L. [US/US]; 107 Balsam Street, Oceanside, NY 11572 (US). CARTIER, Philippe [FR/FR]; 19 rue du General Foy, F-75008 Paris (FR). DE ZIEGLER, Dominique [FR/FR]; 6, rue de la Source, F-75016 Paris (FR).</p> <p>(74) Agents: KOCH, Robert, J. et al.; Fulbright & Jaworski L.L.P., 801 Pennsylvania Avenue, N.W., Washington, DC 20004-2604 (US).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments:</i></p>	

(54) Title: **EXTENDED RELEASE BUCCAL BIOADHESIVE TABLET**

(57) Abstract

A bioadhesive tablet wherein the active ingredient may be protected from water or the surrounding environment, thereby protecting it from metabolism or from other degradation caused by moisture, enzymes, or pH effects, and making it bioavailable only at a controlled rate. The active ingredient may be protected from moisture during the manufacturing process and more importantly may be protected from moisture and the immediate septic environment until after the patient has applied the tablet, and then only at a slow and controlled rate. It is by this process of progressive hydration that the active ingredient remains protected for many hours after administration. It is also by the process of progressive hydration that controlled and sustained release is achieved because only that part of the active ingredient that is the hydrated (aqueous) fraction of the tablet is available for absorption (bioavailable).

BIOADHESIVE PROGRESSIVE HYDRATION TABLET**A****B****C****D****E****F**

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

EXTENDED RELEASE BUCAL BIOADHESIVE TABLET**BACKGROUND OF THE INVENTION****1. Field of the Invention**

5 The present invention relates to a bioadhesive, bioerodible tablet for the extended and controlled release of active ingredients. More particularly, the present invention relates to a progressive hydration tablet for adhesion to the wall of a body cavity for the sustained release of active ingredients without premature degradation of the active ingredients caused by
10 metabolism, or by moisture, enzymes or pH effects.

2. Description of the Related Art

Medications and other pharmaceutical products have traditionally been administered in doses via oral ingestion, nasal sprays or injections. These delivery methods have proven ineffective for patients needing a prolonged and constant supply of an active ingredient delivered
15 to the bloodstream. Particularly difficult are patients needing dosing during sleep time hours. For these patients, intravenous venous lines, slow-dissolving pills, and suppositories or transdermal patches have been prescribed. However, the inconvenience and discomfort of IVs, the short life span of many ingested active ingredients from gastrointestinal degradation or first-pass liver metabolism, and the inability of many products to be comfortably delivered
20 transdermally in suitable doses or in controlled concentrations have proven these methods unsatisfactory.

Previous artisans have attempted to meet the needs of the art by developing products for the transmucosal administration of active ingredients. For example, certain active ingredients can be administered quickly into the bloodstream via the walls of a body cavity, such as the

buccal or vaginal cavities, without the risk of first pass hepatic degradation. Generally, delivery of active ingredients through mucosal surfaces may be enhanced by the use of bioadhesive formulations. However, one particular area where those in the art have attempted, but heretofore failed, to meet the needs of the art is in developing a bioadhesive tablet useful for sustained release applications without risking degradation of the active ingredient before it is actually released.

"Sustained release" generally refers to continuous or sporadic release of an active ingredient over an extended time after a single administration, whereby the level of active ingredient available to the host patient often is maintained at some constant level over a period of time. As used herein, it is also intended to cover the situation where the release of an active ingredient is controlled over a period at time wherein the level of active ingredient available to the host (bioavailable) may be at a variable but predetermined level at a particular instant in time of treatment.

The sustained release bioadhesive tablets known in the art can be generally broken down into two categories: (1) tablets consisting of water soluble carbomers, and (2) tablets consisting of insoluble polymers. Both types of tablets have proven unsatisfactory for many applications. For example, numerous artisans have attempted to formulate a suitable sustained release bioadhesive tablet from water soluble carbomers, such as carbomer 934P or CARBOPOL™ 974 resin (commercially available from B.F. Goodrich, Cleveland, Ohio). However, such tablets often are only able to adhere to the wall of a body cavity for short periods of time, e.g., six hours or less. Also, these tablets are easily dislodged from the wall of a body cavity and thus place patients using such tablets buccally at risk of asphyxiation. Furthermore, these prior art tablets inherently become hydrated relatively quickly and thus may prematurely expose the reservoir of

active ingredient to degradation by moisture or by enzymes from the host environment such as from bacteria in the septic oral or vaginal cavities.

Similarly, tablets comprised of insoluble polymers, such as polycarbophil, have proven unsuitable for many applications. For example, although polycarbophil tablets are capable of prolonged attachment to the wall of a body cavity, such tablets do not adhere immediately, making them impractical for certain treatments such a buccal delivery of active ingredients to patients during sleep time hours. Further, such tablets often do not soften sufficiently to provide comfort and imperceptibility, or provide safety from potential aspiration of the tablet.

Furthermore, for example, neither type of prior art tablet is particularly suitable for treating many conditions. As alluded to previously, there are numerous medical conditions in which a sustained and/or controlled release of active ingredient(s) is desired for any of numerous reasons including, for example, to alleviate the impact of first-pass hepatic metabolism of the active ingredient or the risk of premature degradation of the active ingredient by moisture, pH effects, or enzymes, or to attain the comfort and convenience offered by a suitable bioadhesive tablet. Such conditions include, but are not limited to, for example, those needing treatment with an active ingredient that may be, but is not limited to, a glycoprotein, protein, sex hormone, anti-hormone, nitrate, beta-agonist, beta-antagonist, opioid, opioid-antagonist, antidepressant, HMG CoA (3-hydroxy-3-methylglutaryl Coenzyme A) reductase inhibitor, antihistamine, ACE (angiotensin converting enzyme) inhibitor, and/or prostaglandin. Heretofore the art has required such patents to undergo the more invasive and less suitable techniques and methods of delivery described above.

To illustrate the need in the art, consider hypogonadal men, for example. Hypogonadism in man is characterized by a deficiency or absence of endogenous testosterone production.

Abnormally low levels of testosterone may place men at risk of "Andropause", wherein men are at greater risk of cardiovascular disease, Alzheimer's disease, and osteoporosis.

Testosterone has traditionally been used to treat hypogonadal men. However, to be most effective, the treatment must be capable of complete physiologic testosterone replacement.

5 Moreover, the treatment must be capable of providing sustained levels of testosterone through the night, preferably sustaining a peak in the middle of the night. Transdermal testosterone patches typically produce only sub-physiologic levels and thus incomplete relief. Similarly, the prior art buccal tablets hereintofore described would be ineffective or impractical for such sustained testosterone delivery.

10 The hormone testosterone, like many other drugs, including many other proteins and glycoproteins, undergoes high first pass metabolism. Accordingly, as will be appreciated by one of ordinary skill in the art, buccal or vaginal tablets consisting of materials that are incapable of keeping the interior reservoir of the tablet in the dry state for prolonged periods are inherently incapable of preventing dissolution and swallowing or dissolution and rapid absorption through
15 the mucosa of the active ingredient. Furthermore, as will be appreciated by one of ordinary skill in the art, tablets which are unable to quickly adhere to the target area or are able to become dislodged are impractical for treatments which use night-time delivery, such as testosterone treatment.

20 Furthermore, as will be appreciated by one of ordinary skill in the art, the advantages of a sustained release, bioadhesive tablet according to the present invention are not limited to the treatment of hypogonadism in men. For example, patients often require sustained release hormone treatment for various conditions. In addition, other medications, such as steroids for treating such conditions as asthma, involve treatments where desired peak levels are at night

during sleep-time hours. Accordingly, one of ordinary skill in the art will appreciate that there exists a long-felt, yet unresolved, need to develop a bioadhesive, sustained release tablet to overcome the aforementioned needs of the art, including, but not limited to, the delivery of therapeutically effective amounts of an active ingredient which may be metabolized or otherwise degraded by moisture, enzymes, or pH effects, such as glycoproteins, proteins, sex hormones, anti-hormones, nitrates, beta-agonists, beta-antagonists, opioids, opioid-antagonists antidepressants, HMG CoA reductase inhibitors, antihistamines, ACE inhibitors, and/or prostaglandins.

SUMMARY OF THE INVENTION

The present invention meets the aforementioned needs in the art. Accordingly, it is an object of the invention to provide a bioadhesive tablet that adheres immediately or almost immediately to the target tissue area of a body cavity and generally stays attached substantially throughout treatment. In accordance with this aspect of the invention, there is provided a bioadhesive tablet that can stay attached and deliver active ingredients in the buccal cavity for as much as eighteen hours or more. In accordance with a related aspect of the invention, there is provided a bioadhesive tablet that can stay attached and deliver active ingredients vaginally for as much as 72 hours or more.

It is another object of the invention to provide a bioadhesive tablet that progressively hydrates, whereby the inner core of the tablet remains protected from moisture and the surrounding environment. In accordance with this aspect of the invention there is provided a bioadhesive tablet suitable for sustained release use in mucosal and other body cavities even with

active ingredients comprising proteins or glycoproteins or other treating agents that are particularly susceptible to metabolism, or to enzymatic, pH, or moisture-induced degradation.

It is a related object of the invention to provide a bioadhesive tablet having both controlled and sustained release properties due to a tablet formulation wherein the active ingredient is only progressively made bioavailable over an extended time period by the progressive hydration of the tablet's dry reservoir of active ingredient.

It is another object of the invention to provide a bioadhesive tablet according to the invention that also gelifies and/or swells to help protect a patient using the tablet buccally from asphyxiation, particularly a sleeping patient undergoing treatment.

It is yet another object of the invention to provide methods of making bioadhesive tablets in accordance with the aforementioned objects of the invention. In accordance with one aspect of the invention, there is provided a method of making bioadhesive tablets wherein an active ingredient resistant to premature metabolism and/or degradation is added in the first and/or second step (manufacture of granulate). In accordance with a related aspect of the invention there is provided a method of making bioadhesive tablets wherein an active ingredient prone to premature metabolism and/or degradation is added in the second step (manufacture of the tableting mixture) after the granulate is dried and sieved. Of course, other concerns or factors may affect the choice of which step or steps are appropriate for adding a particular active ingredient.

It is yet another object of the invention to provide methods of using bioadhesive tablets as described herein. In accordance with one aspect of the invention, there is provided a method of using a bioadhesive tablet to administer to a male patient a sustained release of testosterone. In accordance with a related aspect of the invention, there is provided a method of using a

bioadhesive tablet to administer to a female patient a sustained release of a hormone, such as testosterone.

The inventors of the present invention have discovered, quite unexpectedly, that these and other objects for the invention may be achieved by making and using tablets comprising an active ingredient, water soluble polymers (e.g., CARBOPOL™ 974P), and insoluble polycarbophil (e.g., NOVEON®, available from B.F. Goodrich Specialty Polymers of Cleveland, OH), and preferably hydroxypropylmethyl cellulose (HPMC), lactose, corn starch and other standard tablets ingredients, such as magnesium stearate and talc.

Bioadhesive, progressive hydration tablets according to the invention may be used with any suitable active ingredient and may be used to deliver a therapeutic amount of the active ingredient to a patient at controlled rates for sustained periods of time. Tablets according to the invention may also be constructed in any suitable shape and any suitable size consistent with the intended therapeutic use of the tablet.

Tablets according to the invention may comprise any suitable amount of active ingredient. Suitable amounts of active ingredient according to the invention are may be from minuscule amounts of active ingredient to about 50%, or more, by weight active ingredient. As will be appreciated by one of ordinary skill in the art, "minuscule amounts" is intended to cover those amounts of active ingredient that are disproportionately small relative to the tablet, for example, when only a few micrograms of active ingredient are to be delivered via a tablet weighing over a hundred milligrams. Accordingly, one of ordinary skill in the art will appreciate that any amount of active ingredient, in any ratio, is within the scope of the present invention.

The balance of the tablet according to the invention may comprise water soluble polymer(s) and water insoluble cross-linked polycarboxylic polymer(s). Also, according to the invention, exemplary tablets preferably have between about 1% and about 75% by weight water soluble polymer and between about .5% and about 10% by weight water insoluble cross-linked polycarboxylic polymer. In accordance with the invention, such exemplary tablets also preferably include between about 5% and about 50% cellulose. Also in accordance with the invention, presently preferred tablets may have between about .5% and about 25% by weight starch. These preferred tablets may also have between about 1% and about 50% by weight lactose.

Furthermore, according to the invention, preferred tablets may comprise from about .01% up to about 2% silica; and/or up to about .5% by weight talc; and/or up to about 2.5% by weight magnesium stearate.

Accordingly, one of ordinary skill in the art will appreciate that the components of the tablets can be varied to suit a particular purpose. For example, the inventors of the present invention have discovered, quite unexpectedly, that one way of increasing (decreasing) the time it takes a progressive hydration tablet to hydrate is by decreasing (increasing) the amount of lactose and/or starch and increasing (decreasing) the amount of water soluble polymer. Alternatively, the density of the tablet may be altered to affect the hydration period.

Active ingredients suitable for use in the present invention include any active ingredient or ingredients requiring sustained or controlled release, any active ingredient or ingredients requiring extended protection from premature degradation of the active by moisture, pH effects, or enzymes, or any active ingredient requiring administration to a patient with protection from first-pass hepatic metabolism. Exemplary active ingredients suitable for use with the present

invention include, but are by no means limited to: (1) glycoproteins, such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (HCG), thyroid-stimulating hormone (TSH), and the like; (2) proteins, such as GnRH (agonist and antagonist), oxytocin analogs, somatostatin analogs, tissue plasminogen activator (TPA), growth hormone releasing hormone (GHRH), corticotropin-releasing hormone analogs (CRH analogs), and the like; (3) sex hormones, such as estradiol, testosterone, progesterone, and the like; (4) anti-hormones, such as tamoxifen, mifepristone, and the like; (5) nitrates, such as nitroglycerin, isosorbide, erythrityl tetranitrate, pentaerythritol tetranitrate, and the like; (6) beta-agonists, such as terbutaline, albuterol, pirbuterol, bitolterol, ritodrine, and the like; (7) beta-antagonists, such as propranolol, metoprolol, nadolol, atenolol, timolol, esmolol, pindolol, acebutolol, labetalol, and the like; (8) opioids, such as morphine, hydromorphone, oxymorphone, codeine, hydrocodone, oxycodone, levorphanol, levallorphan, buprenorphine, fentanyl, nalbuphine, butorphanol, pentazocine, and the like; (9) opioids-antagonists, such as naloxone, nalmefene, and the like; (10) antidepressants, such as amitriptyline, amoxapine, desipramine, doxepin, imipramine, maprotilen, nortriptyline, protriptyline, trimipramine, fluoxetine, trazodone, and the like; (11) HMG CoA reductase inhibitors, such as lovastatin, mevastatin, simvastatin, pravastatin, atorvastatin, and the like; (12) antihistamines, such as loratadine, chlorpheniramine maleate, brompheniramine maleate, diphenhydramine, dimenhydrinate, carbinoxamine, promethazine, triprolidine, and the like; (13) ACE inhibitors, such as captopril, enalapril, lisinopril, and the like; and, (14) prostaglandins, such as misoprostol and the like. Accordingly, one of ordinary skill in the art will appreciate that tablets according to the invention may be used with a wide variety of active ingredients to treat a wide variety of conditions.

The aforementioned and other aspects of the invention will become more clear by reference to the Figures and descriptions of preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a series of photographs depicting the progressive hydration of a
5 bioadhesive tablet according to the invention.

Figure 2 is a flowchart depicting a presently preferred method of making bioadhesive tablets according to the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

A presently preferred embodiment of the invention is depicted in Figure 1. As shown
10 in the first-frame of Figure 1, before the tablet is administered all of the active is in the dry state and thus, not subject to the deleterious action of moisture, pH effects, enzymes or other chemicals. It is also not available for absorption (bioavailable). As shown in frames 2-6 of Figure 1, over time the residual portion of the active remains in the dry state which both protects it from water and the immediate environment as well as allowing it to serve as a
15 reservoir for the sustained and controlled release of the active. Such a delivery system is well suited for the delivery of proteins, glycoproteins, and other drugs which must be protected from metabolism or during prolonged administration from enzymatic, pH, or moisture-induced degradation.

In a preferred embodiment, when used buccally, progressive hydration of the
20 bioadhesive tablet protects the patient, should the tablet become dislodged, by gelifying and becoming heavier and thus less likely to float in the airway, risking aspiration. This makes

this embodiment particularly well suited for agents that should reach their peak levels in the middle of the night, e.g., hormones like testosterone or steroids to treat asthma. According to the invention, the hydration of the tablet can preferably take hours (e.g. 12 to 24 hours) when formulated for buccal tablets or even days when formulated for vaginal use. As will be

5 appreciated by one of ordinary skill in the art, prior art bioadhesive tablets do not protect the active ingredient from moisture, pH, or from enzymes produced by bacteria in the septic oral and vaginal orifices.

Furthermore, as will be appreciated by one of ordinary skill in the art following the teaching of the present application, the tablet can be sized shaped and dosed to meet the needs

10 of the particular treatment being undertaken. For example, the buccal bioadhesive tablet depicted in Figure 1 was constructed to be only 9mm in diameter for the comfort of the patient, but made capable of delivering 7mg of testosterone per day, full physiologic level. By contrast, prior art transdermal patches were only capable of delivering 5mg per day, in other words a sub-physiologic level.

15 A presently preferred method of manufacturing bioadhesive tablets is diagramed in Figure 2. The presently preferred method involves three steps as described below:

1. First step: manufacture of the granulate.

Hydroxypropylmethyl cellulose 15.000(=HPMC 15 000) is mixed with corn starch and lactose and in case of an active ingredient non sensitive to moisture the active is added.

20 The mixture is wet with an aqueous solution of hydroxypropylmethyl cellulose 5 (=HPMC 5) and knead/granulated.

The granulate is dried in an oven under warm air (50°C) until moisture content is less than 2.5%

The dried granulate is broken with a stainless steel sieve oscillating granulator mesh size 1000 μm .

5 2. Second step: manufacture of the tableting mixture. Talc, silicon dioxide magnesium stearate, and in a case of an active sensitive to moisture, the active ingredient is added. All is sieved through a sieving machine having aperture size 500 μm and then transferred into a free-fall mixer.

 Addition of the granulate of step 1, followed by polycarbophil, carbomer and lactose.
10 The whole is mixed until homogenous.

3. Third step: tableting

The tableting mixture is compressed into tablets by means of a rotative tableting machine equipped with punches 9mm flat on the upper side and curved ($r=9\text{mm}$) on the lower side both with beveled edge. The tablets are dedusted and packed.

15 As depicted in Figure 2, an active ingredient that is non-sensitive to moisture is preferably added during the manufacture of the granulate. However, alternatively, the active ingredient can be added during the second step after the granulate is dried and sieved. Also, as will be appreciated by one of ordinary skill in the art, this second method is particularly preferred when the active ingredient is sensitive to moisture.

20 In a presently preferred manufacturing process, the active ingredient is preferably protected from moisture. A wet granulation is made of lactose, corn starch and HPMC.

Testosterone, polycarbophil, carbomer 934P, talc and magnesium stearate are added dry for the final compression.

Furthermore, as will be appreciated by one of ordinary skill in the art following the teaching of the present application, the materials of construction can be varied to optimize the desired characteristics of the tablet. For example, the present inventors have discovered that, quite unexpectedly, by progressively decreasing the amount of lactose and corn starch and progressively increasing the amount of carbomer 934P, the amount of time it takes a tablet to hydrate is progressively increased. Accordingly, as will be appreciated by one of ordinary skill in the art, tablets suited for specific treatments (i.e., specific active, specific dose, specific delivery time) can be manufactured.

These and other aspects of the invention may be more clearly shown by way of example.

EXAMPLE: TESTOSTERONE TABLET

The following is an example of a formulation (Formulation 8, batch #00029906) designed for complete physiologic replacement of testosterone in men:

Testosterone	30.000 mg	24.0%
HPMC	26.250 mg	21.0%
Corn Starch	22.500 mg	18.0%
Monohydrated Lactose	30.125 mg	24.1%
Silica	1.250 mg	1.0%
Polycarbophil (Noveon)	3.125 mg	2.5%
Carbomer 974P	9.375 mg	7.5%

Talc	1.500 mg	1.2%
Magnesium stearate	0.875 mg	0.7%

Formulations like the one above produced sustained release in in-vitro dissolution tests. When used in female subjects formulas like this one also produce a sustained and controlled release of testosterone for 12 hours or more.

Table 1 depicts nine different formulations of bioadhesive tablets according to the invention. The active ingredient, testosterone, was held constant at 30.0 mg (24% by weight) so the effect of varying the proportions of the inactive ingredients could be studied.

The testosterone dissolution rates of selected formulations were then studied. Table 2 depicts the testosterone dissolution rate of six tablets selected from Formula 1, batch #0069904. Table 3 depicts the testosterone dissolution rate of six tablets selected from Formula 3, batch #0049904. Table 4 depicts the testosterone dissolution rate of six tablets selected from Formula 5, batch #0029904. Table 5 depicts the testosterone dissolution rate of Formula 6, batch #0019904.

The dissolution rate data was then graphed to illustrate the percent of testosterone released per hour. Chart 1 depicts the testosterone release rate for Formula 1 (see Table 2). Chart 2 depicts the testosterone release rate for Formula 3 (see Table 3). Chart 3 depicts the testosterone release rate for Formula 5 (see Table 4). Chart 4 depicts the testosterone release rate for Formula 6 (see Table 5).

As shown in the charts and tables, by decreasing the amount of lactose and corn starch and increasing the amount of carbomer 934P, the time it takes for the tablet to hydrate is progressively increased. Formulation 1 (0069904) and others like it with high levels of carbomer 934P and low levels of lactose and corn starch are probably best suited for vaginal administration where release is often required over a period days. In the first example given above Formulation 8 (0029906), where the levels of lactose and corn starch are high and carbomer 934P is low, the formula is probably better suited to buccal administration where 12 hours of delivery is usually sufficient.

As will be appreciated by one of ordinary skill in the art, the examples and preferred embodiments are not intended to be limiting, and the invention applies to tablets comprised of any active ingredient and any combination of tablet materials. Furthermore, as will be appreciated by one of ordinary skill in the art, the invention is intended to cover the methods of manufacturing and therapeutic uses of the aforementioned tablets.

Testosterone KT

	Form. 1		Form. 2		Form. 3		Form. 4		Form. 5		Form. 5		Form. 6		Form. 7		Form. 8		Form. 9	
	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%
Testosterone	30,000	24,00	30,000	24,00	30,000	24,00	30,000	24,00	30,000	24,00	30,000	24,00	30,000	24,00	30,000	24,00	30,000	24,00	30,000	24,00
HPMC 90SH-15000	31,250	25,00	30,000	24,00	28,750	23,00	27,500	22,00	26,250	21,00	26,250	21,00	26,250	21,00	26,250	21,00	26,250	21,00	26,250	21,00
Corn starch	2,500	2,00	7,500	6,00	12,500	10,00	17,500	14,00	22,500	18,00	22,500	18,00	22,500	18,00	22,500	18,00	22,500	18,00	22,500	18,00
Monohydrated lactose	11,375	9,10	13,875	11,10	16,375	13,10	18,875	15,10	21,375	17,10	21,375	17,10	24,500	19,60	27,625	22,10	30,125	24,10	33,250	26,80
Silica	1,250	1,00	1,250	1,00	1,250	1,00	1,250	1,00	1,250	1,00	1,250	1,00	1,250	1,00	1,250	1,00	1,250	1,00	1,250	1,00
Polycarbophil acid (Noveon AA-)	3,125	2,50	3,125	2,50	3,125	2,50	3,125	2,50	3,125	2,50	3,125	2,50	3,125	2,50	3,125	2,50	3,125	2,50	3,125	2,50
Carbomer 974 P	43,750	35,00	37,500	30,00	31,250	25,00	25,000	20,00	18,750	15,00	15,825	12,50	15,825	12,50	12,500	10,00	9,375	7,50	8,250	5,00
Talc	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	1,500	1,20	1,500	1,20
Magnesium stearate	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70	0,875	0,70
Total Weight	125,000	100,00	125,000	100,00	125,000	100,00	125,000	100,00	125,000	100,00	125,000	100,00	125,000	100,00	125,000	100,00	125,000	100,00	125,000	100,00

TABLE 1

TESTOSTERONE DISSOLUTION RATE

BATCH: 0069904
DISSOLUTION APPARATUS: ROTATING PADDLE 60 RPM / PLATINUM WIRE SPHERAL

SAMPLE	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)
	0	1	2	4	6	8	24
1	0.0	0.7	1.9	7.6	10.6	16.0	83.6
2	0.0	0.6	1.7	6.7	11.7	18.0	88.5
3	0.0	0.7	2.0	6.9	11.7	17.9	84.9
4	0.0	0.6	1.7	7.0	11.2	17.1	88.3
5	0.0	0.7	1.9	6.8	10.9	17.0	87.4
6	0.0	0.7	2.1	6.6	12.4	18.3	86.6
AVERAGE VALUE	0.0	0.7	1.9	6.9	11.4	17.4	86.6

TABLE 2

TESTOSTERONE DISSOLUTION RATE

BATCH: 0049904
 DISSOLUTION APPARATUS: ROTATING PADDLE 60 RPM / PLATINUM WIRE SPHAL

SAMPLE	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)
	0	1	2	4	6	8	24
1	0.0	0.9	3.1	5.6	10.6	16.5	83.6
2	0.0	1.1	3.1	5.6	10.5	16.9	82.2
3	0.0	1.2	3.4	6.3	11.8	18.0	83.4
4	0.0	0.9	2.9	5.4	10.8	16.7	82.7
5	0.0	1.1	4.9	5.7	10.6	16.7	83.0
6	0.0	1.0	2.9	5.6	11.0	16.8	83.6
AVERAGE VALUE	0.0	1.0	3.4	5.7	10.9	16.9	83.4

TABLE 3

— CONTINUED —

0029904

BATCH:

BD

0029904 BATCH : DISSOLUTION APPARATUS : ROTATING PADDLE 60 RPM / PLATINUM WIRE SPIRAL							
SAMPLE	WITHDRAW (HOUR) 0	WITHDRAW (HOUR) 1	WITHDRAW (HOUR) 2	WITHDRAW (HOUR) 4	WITHDRAW (HOUR) 6	WITHDRAW (HOUR) 8	WITHDRAW (HOUR) 24
1	0.0	0.9	2.2	5.9	10.8	16.3	80.3
2	0.0	0.9	2.3	6.7	11.8	17.8	87.5
3	0.0	0.9	2.4	6.9	12.3	17.7	75.2
4	0.0	0.9	2.3	6.8	12.4	18.6	82.4
5	0.0	0.9	2.5	6.9	12.9	19.5	83.2
6	0.0	0.9	2.2	6.6	12.2	18.8	86.6
AVERAGE VALUE	0.0	0.9	2.4	6.6	12.1	18.1	82.5

TABLE 4

TESTOSTERONE DISSOLUTION RATE

BATCH: 0019904
DISSOLUTION APPARATUS: ROTATING PADDLE 60 RPM / PLATINUM WIRE SPIRAL

SAMPLE	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)	WITHDRAW (HOUR)
	0	1	2	4	6	8	24
1	0.0	1.2	2.1	5.9	11.1	16.1	71.7
2	0.0	0.8	2.0	5.0	9.7	14.1	70.1
3	0.0	0.9	2.3	6.4	11.3	15.8	74.6
4	0.0	0.9	2.0	5.5	10.4	15.0	68.6
5	0.0	0.8	1.8	4.9	9.9	14.6	76.6
6	0.0	0.9	1.8	4.9	9.1	13.1	70.3
AVERAGE VALUE	0.0	0.9	2.0	5.4	10.3	14.8	72.0

TABLE 5

CHART 1

Formula 1

% of Testosterone released (dissolution / rotating paddle 60 rpm + platinum wire spiral)
single value (n=6) , Batch 0069904

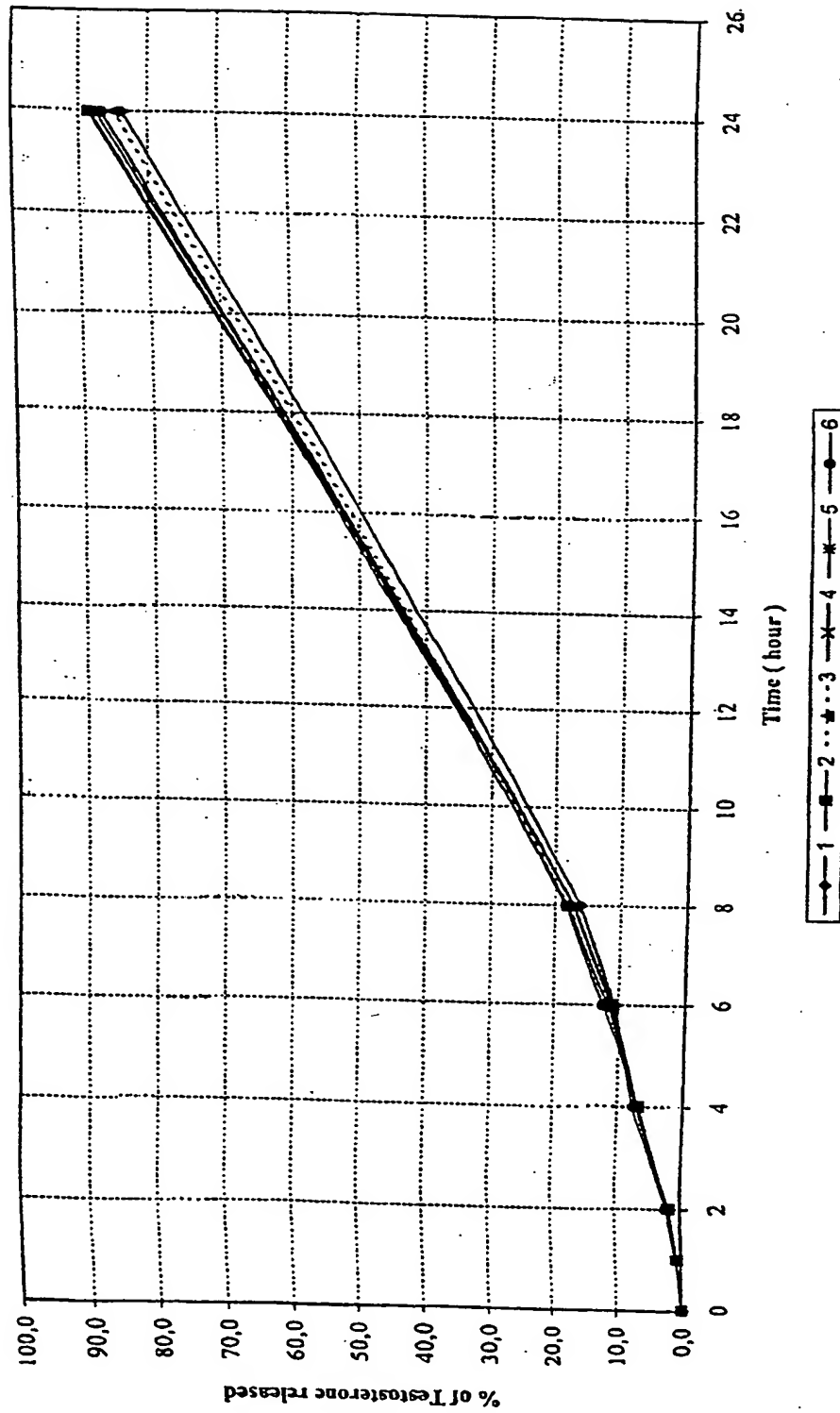


CHART 2

% of Testosterone released (dissolution / rotating paddle 60 rpm + platinum wire spiral)
single value (n=6) , Batch 0049904

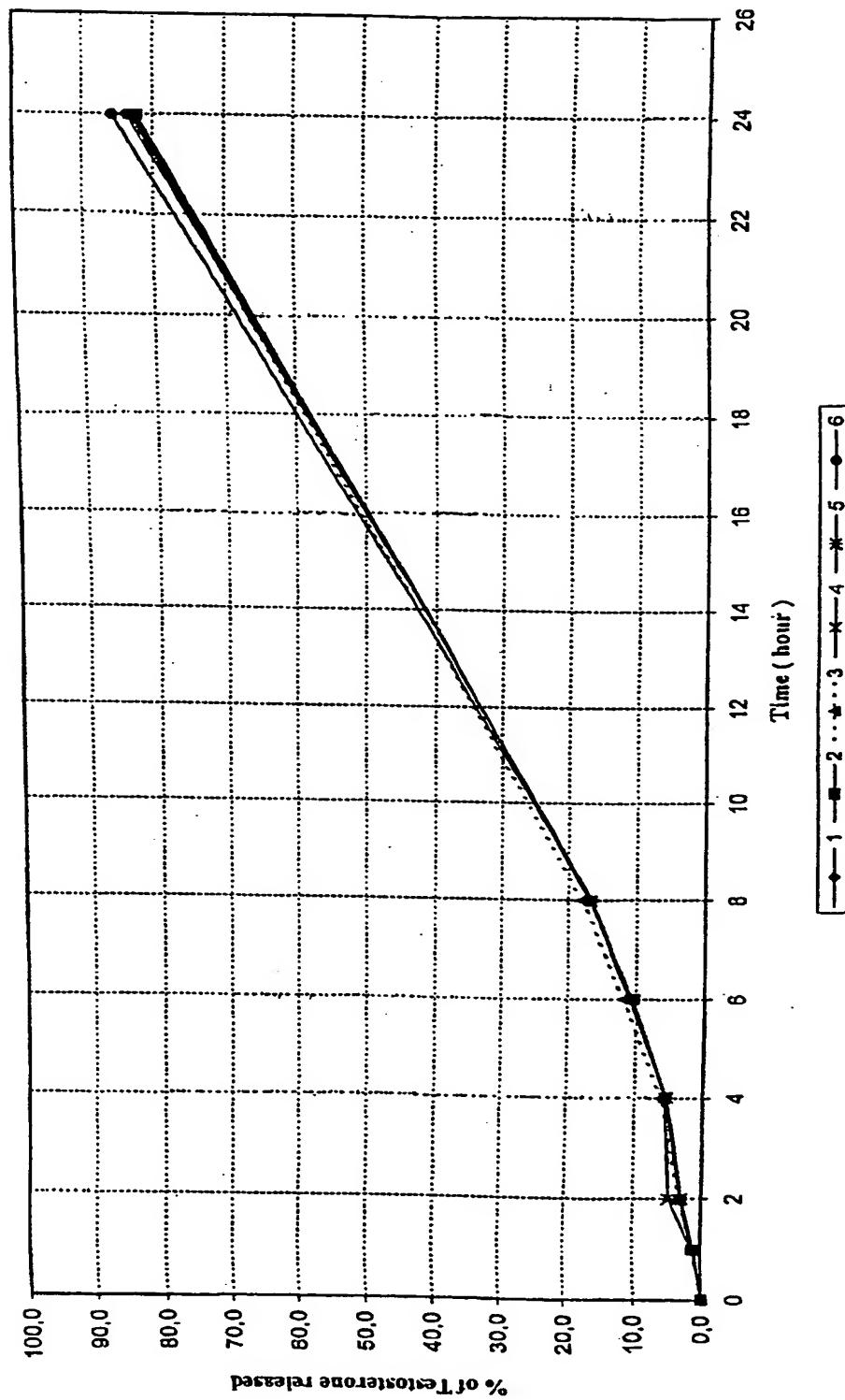


CHART 3

% of Testosterone released (dissolution / rotating paddle 60 rpm + platinum wire spiral)
single value (n=6) , Batch 0029904

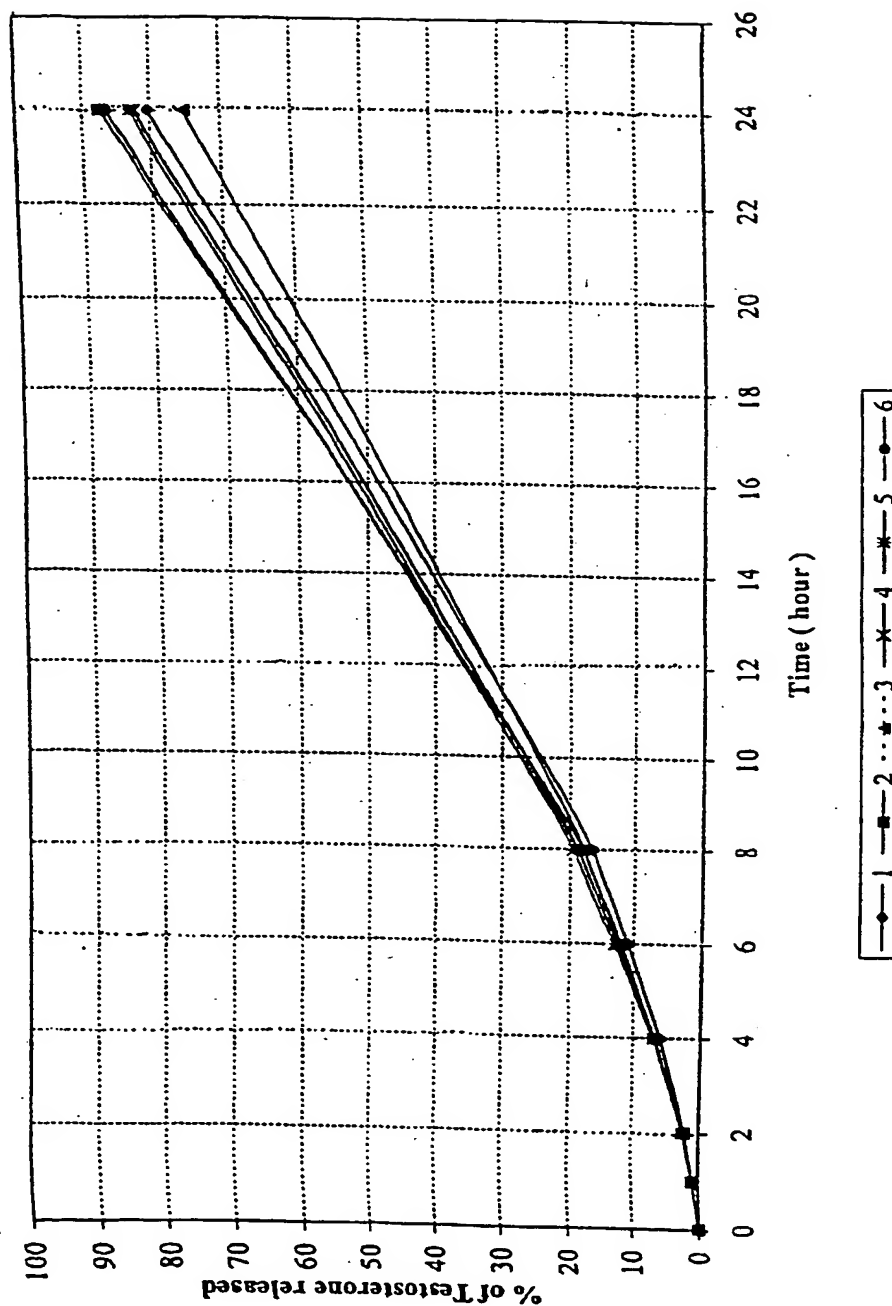
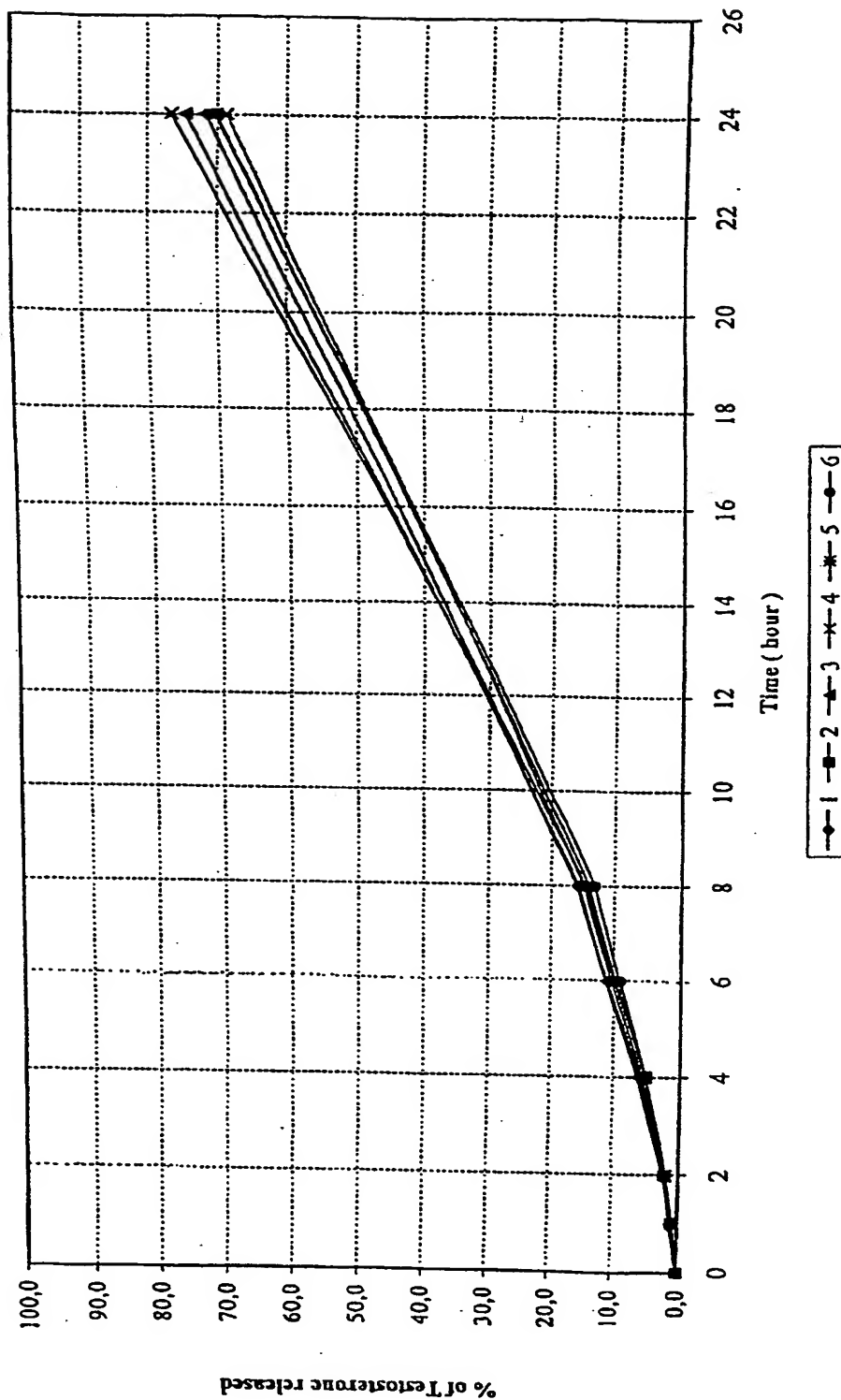


CHART 4

% of Testosterone released (dissolution / rotating paddle 60 rpm + platinum wire spiral)
single value (n=6) , Batch 0019904



WHAT IS CLAIMED IS:

1. A sustained release, progressive hydration bioadhesive tablet comprising:
an effective amount of active ingredient,
about 5% to about 50% by weight cellulose,
about .5% to about 25% by weight starch,
about 1% to about 50% by weight lactose,
about .5% to about 10% by weight water insoluble cross-linked polycarboxylic polymer, and
about 1% to about 75% by weight water soluble polymer.
2. The tablet of claim 1, wherein said tablet comprises between a minuscule amount and about 50% by weight active ingredient.
3. The tablet of claim 2, further comprising:
about 1% by weight silica.
4. The tablet of claim 3, further comprising:
about .5% to about 2% by weight talc.
5. The tablet of claim 4, further comprising:
about .5% to about 1% by weight magnesium stearate.
6. The tablet of claim 1 or 5, wherein said active ingredient is selected from the group consisting of glycoproteins, proteins, sex hormones, anti-hormones, nitrates, beta-agonists, beta-antagonists, opioids, opioid-antagonists, antidepressants, HMG CoA reductase inhibitors, antihistamines, ACE inhibitors, prostaglandins, and any other active ingredient which is metabolized or degraded by moisture, enzymes or pH.

7. The tablet of claim 5, wherein said starch is present in about 2% to about 10% by weight, said lactose is present in about 8% to 16% by weight, and said water soluble polymer is present in about 25% to about 35% by weight, and wherein said tablet is adapted for delivering said active ingredient to the bloodstream of a patient via the patient's vaginal cavity.
8. The tablet of claim 5, wherein said starch is present in about 14% to 24% by weight, said lactose is present in about 17% to 27% by weight, and said water soluble polymer is present in about 5% to about 20% by weight, and wherein said tablet is adapted for delivering said active ingredient to the bloodstream of a patient via the patient's buccal cavity.
9. A sustained release, progressive hydration bioadhesive tablet comprising:
an effective amount of an active ingredient,
about 2% to about 30% by weight binder,
about 5% to about 40% by weight lactose,
about 1% to about 3% by weight water insoluble cross-linked polycarboxylic polymer, and
about 5% to about 50% by weight water soluble polymer.
10. The buccal tablet of claim 9, further comprising:
about .2 to 2% by weight silica.
11. The buccal tablet of claim 10, further comprising:
about .5% to about 2% by weight talc.
12. The tablet of claim 11, further comprising:
about .5% to about 2% by weight magnesium stearate.

13. The buccal tablet of claim 11, wherein said active ingredient is testosterone and said testosterone is present in an amount of about 1% to about 30% by weight.
14. The tablet of claim 13, wherein said starch is present in about 2% to about 10% by weight, said lactose is present in about 8% to 16% by weight, and said water soluble polymer is present in about 25% to about 35% by weight, and wherein said tablet is adapted for delivering said active ingredient to the bloodstream of a patient via the patient's vaginal cavity.
15. The tablet of claim 13, wherein said starch is present in about 14% to 24% by weight, said lactose is present in about 17% to 27% by weight, and said water soluble polymer is present in about 5% to about 20% by weight, and wherein said tablet is adapted for delivering said active ingredient to the bloodstream of a patient via the patient's buccal cavity.
16. A method of delivering an active ingredient to a person comprising sustained release administration of an active ingredient via a progressive hydration bioadhesive tablet.
17. The method of claim 16 wherein the bioadhesive tablet comprises a water insoluble but water-swellaable cross-linked polycarboxylic polymer, a water soluble polymer and testosterone.
18. A method of treating or preventing ischemia or Alzheimer's disease comprising administering to a patient a therapeutically effective amount of testosterone via a sustained release, progressive hydration bioadhesive tablet.
19. The method of claim 18 wherein the bioadhesive tablet is a buccal tablet comprising a water insoluble cross-linked polycarboxylic polymer, a water soluble polymer and testosterone.

20. The method of claim 18, wherein the bioadhesive tablet is a vaginal tablet comprising a water insoluble cross-linked polycarboxylic polymer, a water soluble polymer and testosterone.
21. A sustained release, progressive hydration bioadhesive tablet for delivering an active ingredient to the bloodstream of a patient to treat a health condition, comprising a therapeutically effective amount of an active ingredient, a water insoluble cross-linked polycarboxylic polymer, and a water soluble polymer.
22. Use of an active ingredient together with a water insoluble cross-linked polycarboxylic polymer and a water soluble polymer for the preparation of a sustained release, progressive hydration bioadhesive tablet for delivering an active ingredient to the bloodstream of a patient to treat a health condition.

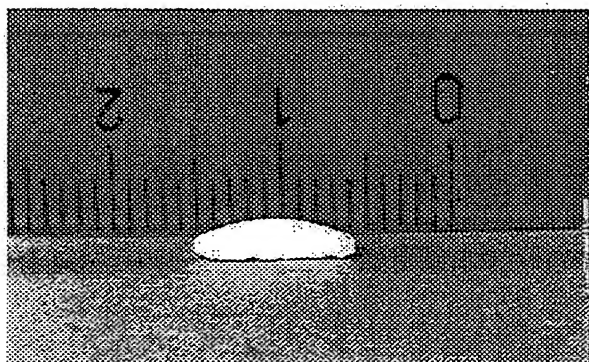


FIG. 1A

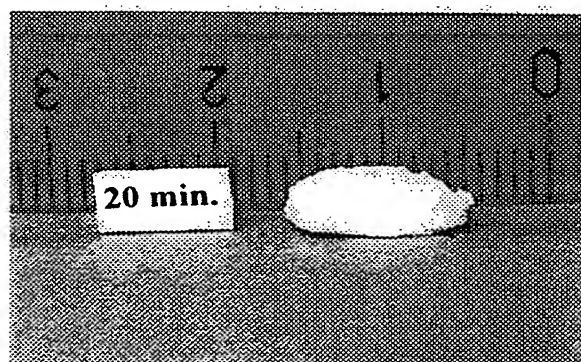


FIG. 1B

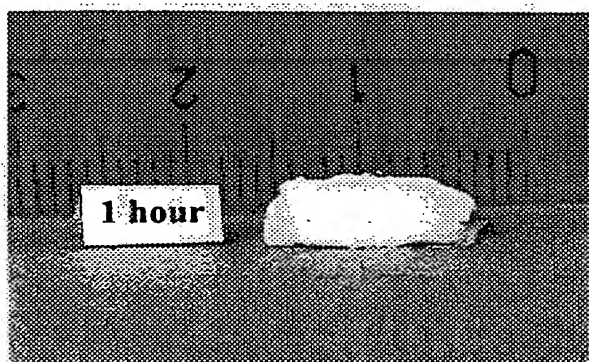


FIG. 1C

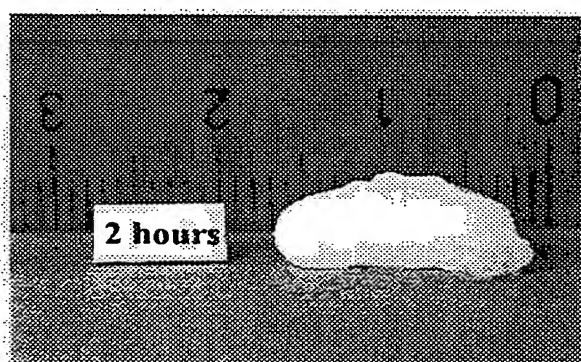


FIG. 1D

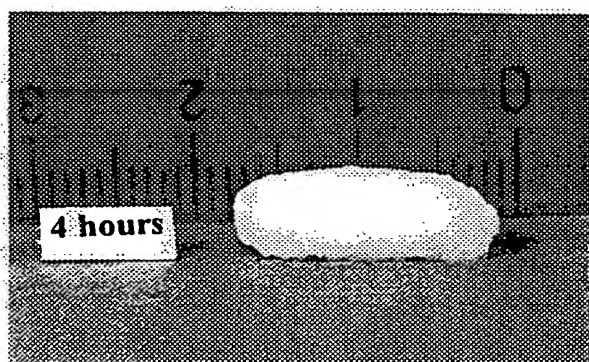


FIG. 1E

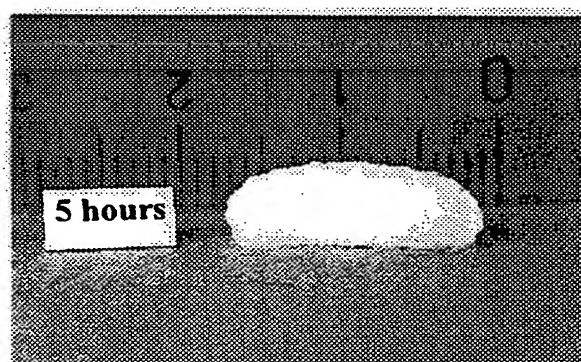


FIG. 1F

2/2

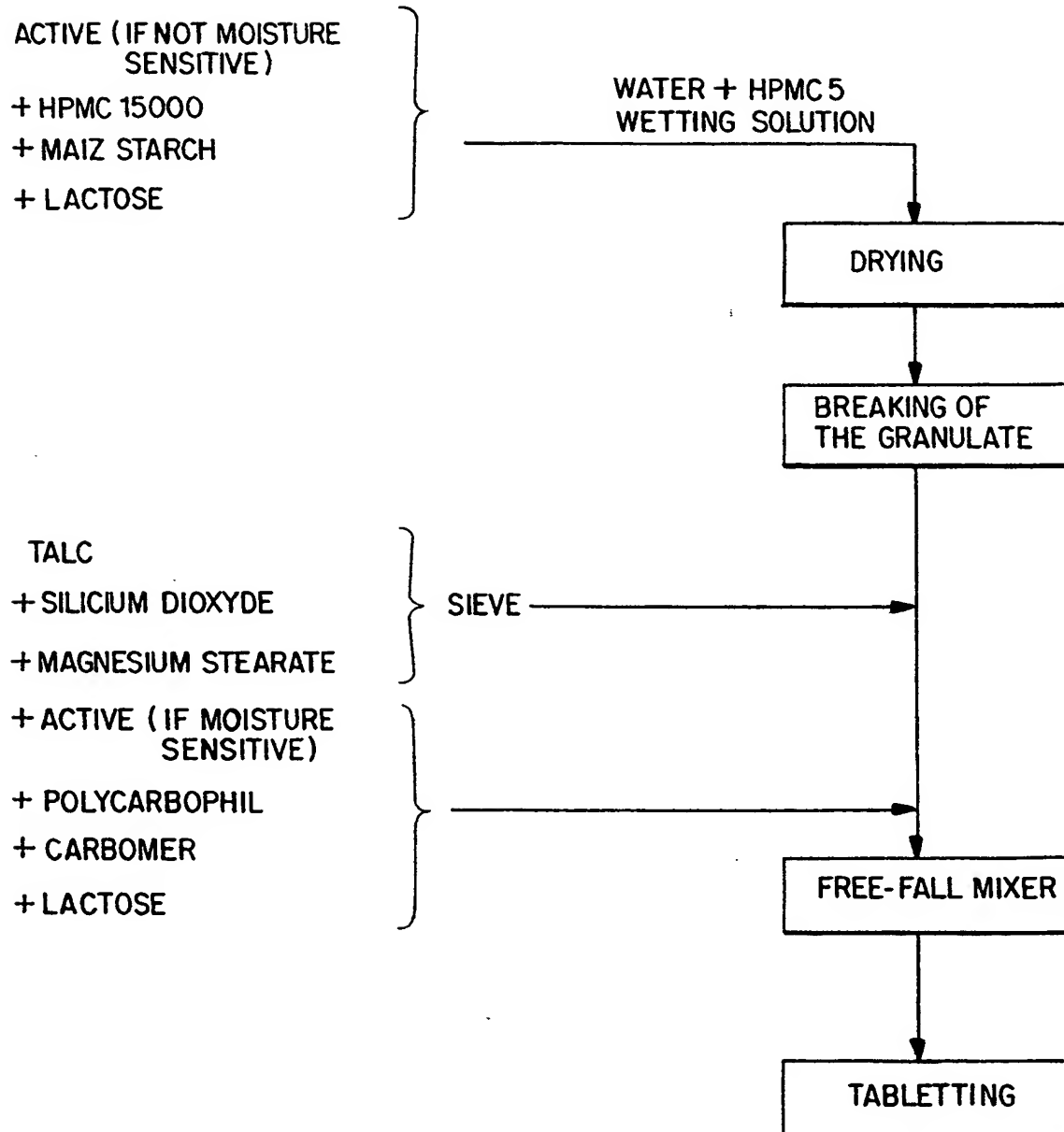


FIG. 2

INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/US 99/19260

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VOORSPOELS J ET AL: "BUCCAL ABSORPTION OF TESTOSTERONE AND ITS ESTERS USING A BIOADHESIVE TABLET IN DOGS" PHARMACEUTICAL RESEARCH, US, NEW YORK, NY, vol. 13, no. 8, August 1996 (1996-08), pages 1228-1232, XP000865566 ISSN: 0724-8741 page 1228	16-19
X	EP 0 159 604 A (TOYO BOSEKI) 30 October 1985 (1985-10-30) page 33 -page 36	16
A		1-15, 17-19
X	EP 0 654 261 A (VETOQUINOL SA) 24 May 1995 (1995-05-24) page 4; example 1	16
A		1-15, 17-19

-/-

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 February 2000

Date of mailing of the international search report

10/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Boulois, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/19260

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	US 4 226 848 A (MACHIDA YOSHIHARU ET AL) 7 October 1980 (1980-10-07) column 7, line 44 - line 63 claims	16
A	EP 0 488 139 A (HOKURIKU PHARMACEUTICAL) 3 June 1992 (1992-06-03) page 7; example 18	1-18
A	PATENT ABSTRACTS OF JAPAN vol. 018, no. 371 (C-1224), 13 July 1994 (1994-07-13) & JP 06 100466 A (TSUMURA & CO), 12 April 1994 (1994-04-12) abstract	18,19

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 19260

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 16-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/19260

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0159604	A	30-10-1985	JP 1832298 C	29-03-1994
			JP 5030808 B	11-05-1993
			JP 60215622 A	29-10-1985
			JP 1504244 C	28-06-1989
			JP 60248609 A	09-12-1985
			JP 63047687 B	26-09-1988
			US 4740365 A	26-04-1988
EP 0654261	A	24-05-1995	FR 2712807 A	02-06-1995
			CA 2136404 A	25-05-1995
			US 5723143 A	03-03-1998
US 4226848	A	07-10-1980	JP 1623175 C	25-10-1991
			JP 2042810 B	26-09-1990
			JP 55118413 A	11-09-1980
			CH 638987 A	31-10-1983
			DE 2908847 A	11-09-1980
			FR 2450610 A	03-10-1980
			GB 2042888 A,B	01-10-1980
			US 4250163 A	10-02-1981
EP 0488139	A	03-06-1992	AT 125447 T	15-08-1995
			CA 2055905 A,C	30-05-1992
			DE 69111574 D	31-08-1995
			DE 69111574 T	18-01-1996
			ES 2077144 T	16-11-1995
			JP 2609022 B	14-05-1997
			JP 5246861 A	24-09-1993
JP 06100466	A	12-04-1994	US 5213806 A	25-05-1993
			NONE	

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (US)